

DIALOGUES



IN CONTRACEPTION®

In This Issue

Contraception for the Woman With Medical Problems

Leon Speroff, MD
Professor of Obstetrics
and Gynecology
Oregon Health & Science University
Portland, Oregon



Grant/Research Support: Organon Inc., Warner Chilcott PLC, Wyeth Pharmaceuticals. *Consultant:* Barr Laboratories.

Andrew M. Kaunitz, MD
Professor and Assistant Chairman
Department of Obstetrics
and Gynecology
University of Florida College
of Medicine—Jacksonville
Jacksonville, Florida



Grant/Research Support: Barr Laboratories, Berlex Laboratories, Johnson & Johnson, National Institutes of Health. *Speaker and Consultant:* American College of Obstetricians and Gynecologists, Association of Reproductive Health Professionals, Barr Laboratories. *Consultant:* Berlex Laboratories, Johnson & Johnson, Pfizer Inc, Procter & Gamble. *Stockholder:* Noven Pharmaceuticals, Inc., Roche Pharmaceuticals, Sanofi-Aventis Pharma, LTD.

Contraceptive Use in Women With Premenstrual Disorders

Kathryn M. Andolsek, MD, MPH
Professor
Department of Community and
Family Medicine
Associate Director
Graduate Medical Education
Duke University Medical Center
Durham, North Carolina



No financial arrangement or affiliation to report.

Andrea J. Rapkin, MD
Professor
Department of Obstetrics and
Gynecology
David Geffen School of
Medicine, UCLA
Los Angeles, California



No financial arrangement or affiliation to report.

Produced by:



under an unrestricted educational grant from



Contraception for the Woman With Medical Problems

Leon Speroff, MD, and Andrew M. Kaunitz, MD

Educational Objectives:

The health care provider should be able to:

- recognize that increased risks are associated with pregnancy in women with various medical conditions
- evaluate evidence-based risks and benefits of use of hormonal contraceptive methods and intrauterine contraceptives (IUCs) in women with various medical conditions
- facilitate use of contraceptive choices that do not exacerbate medical problems

All contraceptive methods currently available in the United States are generally safe for use by healthy, nonsmoking women and pose only minimal health risks overall. Nevertheless, in selecting appropriate contraception for women with existing medical conditions, clinicians must consider that effective contraception is particularly important for many such women because unplanned pregnancy may exacerbate the underlying condition. At the same time, the preexisting condition is itself likely to increase the risks of maternal and fetal complications, morbidity, and mortality inherent in any pregnancy. Therefore, when selecting one of the many effective contraceptive methods available, clinicians and women need to consider each method's risk/benefit profile relative to the specific underlying illness. Risks of pregnancy in women with certain medical conditions are generally greater than risks associated with contraceptive use.

When selecting one of the many effective contraceptive methods available, clinicians and women need to consider each method's risk/benefit profile relative to the specific underlying illness.

This *Dialogues in Contraception*® article addresses a number of common medical problems, describing

the current evidence regarding appropriate hormonal and nonhormonal contraceptive selections. The American College of Obstetricians and Gynecologists (ACOG) issued updated guidelines in June 2006 for the use of hormonal contraception in women with medical conditions¹; the *Dialogues in Contraception*® recommendations are consistent with the updated ACOG guidelines.

Effects of Contraceptive Hormones

Estrogen-containing (combination) methods.

Exogenous estrogen increases synthesis of several coagulation factors that promote thrombosis, in a dose-dependent manner.²⁻⁴ A small increased risk of venous thrombosis and embolism (VTE) is associated with use of combination oral contraceptives (COCs) in women without other risk factors for cardiovascular disease (CVD) compared with nonuse, but the absolute risk of VTE remains very low.^{5,6} Other estrogen-containing contraceptive methods (transdermal patch, vaginal ring) produce pharmacologic estrogen levels and are expected to have an increased risk of VTE similar to COCs.⁷ There is no increased risk of arterial thrombosis (myocardial infarction [MI], stroke) in nonsmoking, normotensive women using these methods compared with nonusers.⁷⁻¹² However, in women with preexisting thrombotic risk factors the risk of thrombosis is further increased by combination hormonal method use.^{13,14}

Progestin-containing methods. Most evidence indicates that progestins have no effect on coagulation factors and therefore no thrombophilic effects.¹⁵⁻¹⁷ As the thrombophilic effect of combination hormonal methods is produced by the estrogen component, progestin-only contraceptive methods (depot medroxyprogesterone acetate [DMPA], etonogestrel [ENG] implant, progestin-only OC, levonorgestrel-releasing intrauterine

Physicians will read the newsletter and submit a Post-Test and Evaluation

Estimated time for completion of activity: 1.5 hours

Release Date: December 2006

Termination Date: December 31, 2009

Available online at www.usc.edu/cme

EDITORIAL BOARD

Executive Editor

DANIEL R. MISHALL, Jr, MD
The Lyle G. McNeile Professor
Department of Obstetrics and Gynecology
Keck School of Medicine
University of Southern California
Los Angeles, California

Associate Editors

KATHRYN M. ANDOLSEK, MD, MPH
Professor
Department of Community and Family Medicine
Associate Director
Graduate Medical Education
Duke University Medical Center
Durham, North Carolina

RAQUEL D. ARIAS, MD
Associate Dean
Associate Professor
Department of Obstetrics and Gynecology
Keck School of Medicine
University of Southern California
Los Angeles, California

RONALD T. BURKMAN, MD
Chairman, Department of Obstetrics and Gynecology
Baystate Medical Center
Springfield, Massachusetts
Deputy Chairman and Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Tufts University School of Medicine
Boston, Massachusetts

PHILIP D. DARNEY, MD, MSc
Professor and Chief
Obstetrics, Gynecology and Reproductive Sciences
San Francisco General Hospital
University of California, San Francisco
San Francisco, California

ANDREW M. KAUNITZ, MD
Professor and Assistant Chairman
Department of Obstetrics and Gynecology
University of Florida College of Medicine—Jacksonville
Jacksonville, Florida

SHARON M. SCHNARE, RN, FNP, CNM, MSN, FAANP
Clinical Instructor
Department of Family and Child Nursing
University of Washington
Seattle School of Nursing
Seattle, Washington

LEE P. SHULMAN, MD
Professor and Chief
Division of Reproductive Genetics
Northwestern University Feinberg School of Medicine
Chicago, Illinois

DEBORAH M. SMITH, MD, MPH
Clinical Associate Professor of Obstetrics and Gynecology
Howard University College of Medicine
Washington, DC

LEON SPEROFF, MD
Professor of Obstetrics and Gynecology
Oregon Health & Science University
Portland, Oregon

CAROLYN L. WESTHOFF, MD, MSc
Director, Division of Family Planning and Preventive Services
Professor of Obstetrics and Gynecology
Professor of Epidemiology and Population & Family Health
Columbia University Medical Center
New York, New York

SUSAN J. WYSOCKI, RNC, NP, FAANP
President and CEO
National Association of Nurse Practitioners in Women's Health
Washington, DC

The *Dialogues in Contraception*® Editorial Board recommends that before using or prescribing any drug discussed in this newsletter, physicians review the full product information.

Disclosure Statement Information

Editorial Board

RAQUEL D. ARIAS, MD *Consultant:* Barr Laboratories, Berlex Laboratories, Novo Nordisk Inc., Ortho-McNeil Pharmaceutical, Inc, Organon Inc., Pfizer Inc, Synova Healthcare Group, Inc., Wyeth Pharmaceuticals.

RONALD T. BURKMAN, MD *Consultant:* Barr Laboratories, Ortho-McNeil Pharmaceutical, Inc., Pfizer Inc. *Speakers' Bureau for Commercial Sponsors:* Berlex Laboratories, FEI Women's Health, LLC, Ortho-McNeil Pharmaceutical, Inc. *Honoraria:* Berlex Laboratories, FEI Women's Health, LLC, Ortho-McNeil Pharmaceutical, Inc.

PHILIP D. DARNEY, MD, MSc *Speakers' Bureau for Commercial Sponsors:* Berlex Laboratories, FEI Women's Health, LLC, Organon Inc.

DANIEL R. MISHALL, Jr, MD *Grant/Research Support:* Berlex Laboratories. *Consultant:* Barr Laboratories, Berlex Laboratories. *Speakers' Bureau for Commercial Sponsors:* Berlex Laboratories.

SHARON M. SCHNARE, RN, FNP, CNM, MSN, FAANP *Consultant:* Barr Laboratories, GlaxoSmithKline, Ortho-McNeil Pharmaceutical, Inc., Procter & Gamble Pharmaceuticals, 3M Pharmaceuticals. *Speakers' Bureau for Commercial Sponsors:* Berlex Laboratories, FEI Women's Health, LLC, Organon Inc., Ortho-McNeil Pharmaceutical, Inc., Pharmacia Corporation, Wyeth Pharmaceuticals.

LEE P. SHULMAN, MD *Grant/Research Support:* Wyeth Pharmaceuticals. *Consultant:* Berlex Laboratories, Ortho-McNeil Pharmaceutical, Inc. *Honoraria:* Berlex Laboratories, GlaxoSmithKline, Ortho-McNeil Pharmaceutical, Inc., Roche Pharmaceuticals, Wyeth Pharmaceuticals.

DEBORAH M. SMITH, MD, MPH No financial arrangement or affiliation to report.

CAROLYN L. WESTHOFF, MD, MSc *Grant/Research Support:* Barr Laboratories, Danco Laboratories LLC, Organon Inc., Organon Inc., Ortho-McNeil Pharmaceutical, Inc. *Consultant:* Barr Laboratories, Inc., Organon Inc. *Speakers' Bureau for Commercial Sponsors:* Organon Inc.

SUSAN J. WYSOCKI, RNC, NP, FAANP *Speakers' Bureau:* Berlex Laboratories, Duramed Pharmaceuticals, Inc., Merck & Co, Inc., Organon Inc., Ortho-McNeil Pharmaceutical, Inc., 3M Pharmaceuticals, Wyeth Pharmaceuticals.

system [LNG-IUS]) may be more appropriate than estrogen-containing methods for women with CVD risk factors.^{1,18} The highly effective copper T380A intrauterine contraceptive (IUC) contains no hormones and therefore also is an appropriate contraceptive option for many women with medical problems that contraindicate use of hormonal contraceptives.

Efficacy/Safety of Contraceptives in Various Medical Conditions

Conditions Associated With Increased Risk of CVD

Diabetes. In women with either type 1 or type 2 diabetes without vascular disease, use of combination hormonal contraception does not adversely affect metabolic control, promote vascular disease, or increase risk of CVD.^{19–24} Use of combination hormonal contraceptive methods does not increase risk of type 2 diabetes in women with prior gestational diabetes.²⁵ In women with diabetes with vascular involvement, use of combination hormonal contraceptive methods is contraindicated.^{26–28} Based on theoretical concerns, ACOG recommends that use of combination hormonal contraceptives in women with diabetes should be limited to nonsmoking, otherwise healthy women who are younger than 35 and have no evidence of hypertension, nephropathy, or retinopathy.¹ For women with diabetes, with or without vascular disease or hypertension, use of IUCs or progestin-only contraceptive methods is not contraindicated.^{18,29,30}

In women with either type 1 or type 2 diabetes without vascular disease, use of combination hormonal contraception does not adversely affect metabolic control, promote vascular disease, or increase risk of CVD.

Hypertension. A systematic review of 22 articles published through February 2005 describing 13 studies of COC use and CVD risk found that, overall, hypertensive COC users were found to be at higher risk for MI and stroke than hypertensive non-COC users, but that women who had their blood pressure measured before initiating COCs were at lower risk for ischemic stroke and MI than women who did not have such pre-initiation measurement.³¹ Because the risks of adverse events in pregnancy are increased in hypertensive women, ACOG recommends that nonsmoking women with blood pressure well controlled by antihypertensive agents, under age 35, and otherwise healthy may try combination hormonal contraceptive methods with careful monitoring; if blood pressure remains controlled, use can be continued.^{1,18} Use of combination hormonal methods in women with severe (ie, uncontrolled) hypertension is contraindicated.^{26–28}

Progestin-only methods and IUCs are appropriate options for women with either controlled or uncontrolled hypertension.^{1,18}

Inherited/acquired thrombophilias. The influence of exogenous estrogen on clotting mechanisms may synergistically further increase risk of thrombosis in women with thrombophilias^{32,33}; therefore, women with known inherited or acquired thrombophilias should not use estrogen-containing contraceptives.¹⁸ Progestin-only contraceptive methods and IUCs are appropriate options. Use of estrogen-containing contraceptives is also contraindicated in women with a personal history of thromboembolic disease,^{27,28,34} but progestin-only contraceptive methods and IUCs are appropriate alternatives.¹ However, ACOG states that individualized decisions may be made regarding use of combination hormonal methods by such women,¹ if they are receiving anticoagulant therapy. This approach seems reasonable, as the small thrombophilic effect of estrogen is overcome by anticoagulant therapy.

Routine testing for thrombophilic factors in asymptomatic women before contraceptive selection is not indicated,^{18,35,36} unless there is a strong family history of thrombophilia (eg, idiopathic VTE in a first-degree relative).^{37,38} Most women with thrombophilias will not develop VTE whether or not they use exogenous estrogen, and risk of VTE in pregnancy is higher for these women than that associated with combined hormonal contraception.^{33,36,39,40} Screening tests for coagulation disorders have poor positive predictive value for clinical events and may exclude many women who could safely benefit from use of hormonal contraception.^{36,38}

Mitral valve prolapse. Asymptomatic mitral valve prolapse is not a contraindication to use of combination hormonal contraceptive methods. However, mitral valve regurgitation, arrhythmia, valve replacement, or the presence of other clinical symptoms precludes use of estrogen-containing methods, which could increase risk of VTE. Progestin-only methods and IUCs are appropriate options.

Obesity. Data are conflicting regarding whether obesity may decrease efficacy of some combination hormonal contraceptives. One study of COC use⁴¹ and one of transdermal patch use⁴² have found somewhat higher pregnancy rates in overweight and obese women. However, in a study of a COC containing ethinyl estradiol (EE) 25 mcg/norgestimate, no significant differences in pregnancy rates were observed between women in the lowest weight decile (86 to 113.5 pounds) and the highest weight decile (175 to 240 pounds).^{43,44} A study of 1 year's use of a 91-day extended-regimen COC (EE 30 mcg/LNG) reported no pregnancies among women weighing 90 kg or more at baseline although pregnancies occurred in women with lower baseline weights.⁴⁵ Similarly, an analysis of vaginal ring data found that no pregnancies occurred in the heaviest women (189 to 272 pounds), including 41 women who weighed 198 pounds or more.⁴⁶ Therefore, it appears that the contraceptive efficacy of combination hormonal methods is sufficiently high in overweight women, and those motivated to use these methods should

not be excluded from doing so.¹ However, obese women should be made aware that obesity, age, and use of estrogen-containing contraceptives are independent risk factors for VTE. ACOG recommends that for obese women aged over 35 progestin-only methods and IUCs represent appropriate contraceptive options.¹

Obese women should be made aware that obesity, age, and use of estrogen-containing contraceptives are independent risk factors for VTE. ACOG recommends that for obese women aged over 35 progestin-only methods and IUCs represent appropriate contraceptive options.

Temporary or prolonged immobilization. Estrogen-containing methods should be discontinued 1 month prior to elective surgery associated with an increased VTE risk, and not restarted until 1 month post-surgery, to avoid further increasing perioperative risk of thrombosis. Although there are no data to support the recommendation, progestin-only contraceptive methods or IUCs are appropriate for use in women who are paraplegic or otherwise immobilized by disease or injury.

Migraine headaches. Use of combination hormonal contraceptives is contraindicated in women with migraine headaches accompanied by aura (ie, focal neurological symptoms).^{1,18,27,28,47} Many studies of COC use, stroke risk, and migraines do not distinguish migraine with aura from migraine without aura; therefore, there is still a concern as to whether all migraineurs have an increased risk of stroke with use of combination hormonal contraceptives.¹ ACOG guidelines state that combination hormonal methods may be used by women with migraine headaches who do not have focal neurologic symptoms, do not smoke, are otherwise healthy, and are younger than age 35.¹ Progestin-only methods are appropriate options for women with migraine with aura who have no other risk factors for stroke (eg, smoking, hypertension).^{1,18} IUCs may be used by women with migraine with or without aura.^{1,18} For a detailed discussion, see "Relation of Headache to Method of Contraception" in *Dialogues in Contraception*[®], Volume 9, Number 3.

ACOG guidelines state that combination hormonal methods may be used by women with migraine headaches who do not have focal neurologic symptoms, do not smoke, are otherwise healthy, and are younger than age 35.

Other Medical Conditions

Women with seizure disorders. Although decreased contraceptive steroid levels in women taking COCs and some antiepileptic drugs (AEDs) raise concern regarding reduced COC efficacy, no studies have reported higher rates of pregnancy with COC use in women also taking AEDs.¹ Combination hormonal methods are appropriate for use in women with seizure disorders whether or not they are taking enzyme-inducing AEDs or other AEDs. The large Oxford-Family Planning Association contraceptive cohort study found no evidence that combination hormonal methods increase the frequency of epileptic seizures.⁴⁸ Although some authorities recommend using 50-mcg-estrogen COCs in women taking enzyme-inducers, ACOG states that there are no published data supporting this recommendation.¹ Because progestin-only OCs are very low-dose contraceptives, their use would not appear prudent in women using enzyme inducers. A pilot study suggests that the high contraceptive efficacy of the LNG-IUS is maintained in women taking enzyme-inducing drugs.⁴⁹ Product labeling for the ENG implant indicates that this method is not appropriate for women chronically taking enzyme-inducing drugs.⁵⁰ DMPA is a high-dose progestin-only contraceptive, and concomitant use of enzyme inducers has not been found to increase risk of pregnancy in women using this method.⁵¹ In addition, use of DMPA has been found to reduce seizure frequency in women with seizure disorders.⁵²

Systemic lupus erythematosus (SLE). The findings of 2 large randomized trials support the safety of COC use in women with inactive or stable SLE who do not have moderate or high levels of anticardiolipin antibodies.^{53,54} In a 1-year placebo-controlled trial of COCs, rates of severe and moderate disease flares were similar in both treatment groups.⁵³ In a comparative trial of COCs, progestin-only OC, and copper IUC, rates of flares were similar in the 3 treatment groups.⁵⁴ Neither study addressed contraceptive use in women with severe SLE; ACOG recommends that estrogen-containing contraceptives not be used by women with SLE and a history of vascular disease, nephritis, or presence of antiphospholipid antibodies.¹ Progestin-only methods and IUCs are appropriate methods for these women.¹

ACOG recommends that estrogen-containing contraceptives not be used by women with SLE and a history of vascular disease, nephritis, or presence of antiphospholipid antibodies.

Multiple sclerosis (MS). Data from the Nurses' Health Study cohorts indicate that use of COCs is not associated with risk of development of MS (past users, relative risk [RR] 1.2, confidence interval [CI] 0.9-1.5; current users, RR 1.0, CI 0.6-1.7) compared with never-users.⁵⁵ A recent questionnaire study of MS symptoms in pregnancy, postpartum, and COC use found no change in symptoms among 64% of pregnant women, 59% of postpartum women, and 67% of COC ever-users.⁵⁶ No COC users reported worsening of symptoms, and 13% reported symptom improvement, suggesting that there is no progression and possible amelioration of MS during combination hormonal contraceptive use. Progestin-only contraceptive methods and IUCs are also appropriate options for women with MS.

Sickle cell disease (SCD). Progestin-only methods and IUCs are appropriate contraceptive options for women with SCD.^{1,18,57,58} Several studies have found that women with SCD using progestin-only methods (particularly DMPA) had significantly better outcomes (eg, improvements in painful crises, headache, body weakness, biochemical and hematologic parameters) than nonusers with SCD.^{57,58}

The presence of a hemoglobinopathy by itself does not preclude use of combination hormonal contraceptive methods. There are no data regarding VTE risk in women with SCD and COC use. ACOG concludes that pregnancy carries a greater risk for women with SCD than use of combination hormonal contraceptive methods.¹ In the absence of data, combination hormonal contraceptive methods can be used in women with SCD.

Depression and bipolar disorder. In an analysis of data from 17 placebo-controlled trials of women receiving the antidepressant fluoxetine, there was no clinical evidence that concomitant use of COCs and fluoxetine affects the safety or efficacy of either agent.⁵⁹ In a prospective cohort study, depressive symptom scores improved slightly from baseline (method initiation) after 1 year of DMPA use, suggesting that DMPA should not exacerbate symptoms in women with pre-existing depression.⁶⁰ Some women with psychiatric disorders may have difficulty in adhering to daily, weekly, or monthly contraceptive regimens, so IUCs and implantable contraception may be advantageous alternatives. Women with bipolar disorder are sometimes treated with AEDs, so the cautions discussed above (see "Women with seizure disorders") also apply to some women with bipolar disorder. IUCs may be appropriate options for women using AEDs to treat bipolar disorder.

Summary and Conclusions

In women with many medical conditions, pregnancy increases risks of disease exacerbation, comorbidity, and mortality. Such heightened risks underscore the importance of effective contraception to help women with medical conditions avoid pregnancy or delay it until optimal therapeutic control of the underlying condition is achieved. Fortunately, a variety of highly effective contraceptive methods with differing characteristics are available. Clinician familiarity with the benefit/risk profiles of these methods can enhance appropriate selection of contraception for women with various medical conditions.

(continued on page 8)

Contraceptive Use in Women With Premenstrual Disorders

Kathryn M. Andolsek, MD, MPH, and Andrea J. Rapkin, MD

Educational Objectives:

The health care provider should be able to:

- describe common symptoms and diagnostic criteria for premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)
- identify elements of an evidence-based approach to treatment strategies for PMS/PMDD
- understand appropriate contraceptive options for symptom management and/or pregnancy prevention in women with premenstrual disorders

Premenstrual physical and mood symptoms are common among reproductive-age women, but diagnostic criteria and treatment strategies for recognized premenstrual disorders are not always clearly understood. This article addresses the diagnosis and differentiation of premenstrual disorders, as well as various management/treatment approaches, including the use of oral contraceptives for both symptom amelioration and pregnancy prevention.

Definitions of Premenstrual Disorders

Premenstrual disorders are characterized by various cyclic affective and somatic symptoms that occur *only* in ovulatory women and *only* during the luteal phase of the menstrual cycle, resolving within 4 days of the onset of menses.¹ Diagnosis of premenstrual disorders is complicated by the diversity and prevalence of premenstrual symptoms among reproductive-age women: approximately 50% to 80% of women with ovulatory cycles experience at least some premenstrual symptoms that range from mild to severe.² In addition, many medical and psychiatric conditions, such as thyroid disease, diabetes, depressive and anxiety disorders, substance abuse disorders, migraine, asthma, seizure disorders, and endometriosis may be exacerbated during the late luteal or menstrual phase of the cycle.^{1,3} For these reasons, prospective documentation of premenstrual symptoms for at least 2 to 3 cycles is recommended to establish the timing of symptoms relative to menses and to differentiate symptom patterns. Such prospective documentation of symptoms is also necessary to differentiate the more common premenstrual syndrome (PMS), the cyclic luteal phase occurrence of symptoms severe enough to interfere with some aspects of life¹, from the less common premenstrual dysphoric disorder (PMDD), in which the cyclic luteal phase occurrence of symptoms markedly interferes with work or social activities and relationships with others.⁴

PMS

The American College of Obstetricians and Gynecologists (ACOG) criteria state that PMS can be diagnosed if the woman reports *at least 1* of 6 affective symptoms (depression, angry outbursts, irritability, anxiety, confusion, social withdrawal) or *at least 1* of 4 somatic symptoms (breast tenderness, abdominal bloating, headache, swelling of extremities)¹:

- that have occurred during the 5 days before menses in each of the 3 prior menstrual cycles
- are relieved within 4 days of the onset of menses without recurrence until at least cycle day 13
- occur reproducibly during 2 cycles of prospective recording
- and interfere with some part of the woman's normal functioning.

PMDD

Diagnostic criteria for PMDD, as defined by the American Psychiatric Association (APA) in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR), require that, during the last week of the luteal phase in most menstrual cycles during the past year, a

woman experienced at least 5 of the following symptoms, including *at least 1* core symptom⁴:

- core symptoms: depressed mood; anxiety, tension, edginess; marked lability of mood with tearfulness; persistent irritability or anger
- other symptoms: decreased interest in usual activities; difficulty concentrating; fatigue, lethargy; appetite changes; hypersomnia/insomnia; feeling overwhelmed/out of control
- physical symptoms (eg, breast tenderness or swelling, headaches, bloating or weight gain; joint or muscle pain)

Symptoms must begin to remit within a few days after the onset of the follicular phase, be absent in the postmenses period, markedly interfere with work, school, or usual social activities, and be confirmed by prospective daily ratings for at least 2 consecutive cycles.

Epidemiology

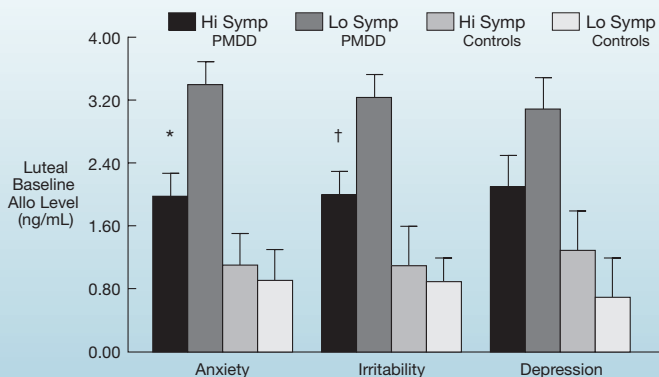
It is estimated that 20% to 40% of reproductive-age women experience premenstrual symptoms that meet the ACOG criteria for PMS.⁵⁻⁷ In addition, about 3% to 9% of reproductive-age women meet the diagnostic criteria for PMDD.⁸⁻¹⁰

Premenstrual disorders can affect women at any stage of reproductive life, beginning with the advent of ovulatory cycles approximately 2 years after menarche (ie, age 14) until menopause (average age 51).² Surveys find that women are most likely to seek treatment after age 30^{1,7} but may have had PMS for about 10 years before seeking treatment.¹¹

Etiology

The etiology of premenstrual disorders is not well understood but appears to be multifactorial.¹ The cyclicality of PMS/PMDD symptoms and their occurrence only in ovulatory women suggests a link with fluctuating gonadal hormone levels associated with ovulation,¹² but there is evidence that in women with premenstrual disorder there are no alterations in circulating levels of any endogenous hormones, including progesterone, compared with controls.¹ However, some—but not all—studies have suggested that alteration of the progesterone metabolite and neuroactive steroid allopregnanolone during the luteal phase in women with PMS/PMDD may contribute to anxiety, tension, and depression (Figure).^{13,14} In addition, alterations in

Figure. Mean (+ SEM) luteal phase baseline plasma allopregnanolone levels in PMDD women and controls as a function of premenstrual symptom severity.¹⁴



* $p < .01$; † $p < .05$.

SEM=standard error of the mean; PMDD=premenstrual dysphoric disorder; ALLO=allopregnanolone; Hi Symp=high symptom severity; Lo Symp=low symptom severity. Adapted with permission from Girdler et al.¹⁴

the renin-angiotensin-aldosterone system may lead to fluid retention and bloating.^{6,12} There is also increasing evidence that luteal phase reductions in serotonin (5-hydroxytryptamine) levels are related to the pathogenesis of PMS/PMDD.¹⁵⁻¹⁷

Diagnosis

In the clinical setting, the timing of premenstrual symptoms can be confirmed with a prospective daily symptom/menstrual period calendar and history kept by the woman for at least 2 to 3 cycles. Encouraging the woman to record symptom types, timing, and severity daily on such a standardized form as the Daily Record of Severity of Problems (DRSP),¹⁸ available on the Internet from the Madison Institute of Medicine at <http://www.pmdf.factsforhealth.org/have/dailyrecord.html>,¹⁹ allows the clinician to confirm that premenstrual symptoms occur only in the luteal phase and disappear just after the onset of menses. In turn, these absolute criteria for PMS/PMDD facilitate exclusion of other diagnoses that could cause symptoms, such as psychiatric disorders, including depressive disorders and anxiety; pain disorders, including dysmenorrhea and endometriosis; and hypothyroidism or other endocrine disorders which may lead to cyclic mastalgia.

Management/Therapy

In order to help reduce the negative impact of premenstrual disorders on a woman's life, treatment should be correlated with the type and degree of symptomatology and the underlying needs of each patient.¹

Nonpharmacologic Interventions

Education about premenstrual disorders, along with reassurance and anticipatory guidance, may relieve anxiety in some women, particularly those with mild-to-moderate symptoms.¹ Knowledge of nonpharmacologic strategies, most of which are considered advantageous to the health of any adult, may also give women with PMS some feeling of control over their condition.

Lifestyle Changes

Increased physical activity, aerobic exercise, stress reduction exercises, and such relaxation techniques as yoga and meditation may enhance mood and reduce premenstrual fluid retention.^{1,3} Cognitive behavioral therapy may be useful alone or in combination with a therapeutic agent to improve symptoms of PMDD.^{20,21}

Addition to the diet of 1000 to 1200 mg/day of calcium carbonate supplementation may help reduce emotional and physical symptoms.¹ A case-control study with the prospective Nurses' Health Study II cohort found that high intake (median 1283 mg/day) of calcium from food sources was significantly inversely related to the risk of developing PMS (multivariate relative risk [RR] 0.70, 95% confidence interval [CI] 0.50-0.97, $p=.02$ for trend) compared with women with the lowest intake (median 529 mg/day).²² ACOG states that vitamin B₆ is of limited clinical benefit in treatment of PMS¹; dosages higher than 100 mg/day may cause harm including irreversible peripheral neuropathy.²³

Pharmacologic Interventions

Addition of a therapeutic agent may be appropriate for women who present with PMDD or severe PMS and for those in whom nonpharmacologic strategies do not sufficiently improve symptoms. The 2 main pharmacologic strategies of treatment are: 1) targeting of central nervous system (CNS) processes believed to contribute to premenstrual mood symptoms; and 2) elimination of hormonal cyclicality by suppression of ovulation. Administration of natural progesterone is not more effective than placebo for treatment of premenstrual disorders.^{1,24}

CNS Agents

Three selective serotonin reuptake inhibitors (SSRIs; fluoxetine 20 mg/day, controlled release paroxetine 12.5 mg/day, sertraline 50 mg/day) are approved by the United States Food and Drug Administration (FDA) for treatment of PMDD.²⁵⁻²⁷ Although these agents are not approved by the FDA for treatment of PMS, systematic reviews of studies of SSRI use in severe PMS and PMDD found SSRIs to be more effective in improving both physical and mood symptoms than placebo.^{28,29} Side effects (including

nausea, insomnia, fatigue, dizziness, gastrointestinal irritability, tremor, sweating, headache, anxiety, decreased libido)^{29,30} are common in individuals who use SSRIs. For this reason, it is appropriate to recommend cyclic SSRI therapy before continuous dosing.²⁸ Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, and anxiolytics (eg, alprazolam, diazepam, buspirone) may also be useful for women with premenstrual disorders. Use of any of the CNS agents for treatment of PMS/PMDD does not contraindicate concomitant use of any hormonal or nonhormonal contraceptive method to prevent pregnancy. A retrospective analysis of data from the US fluoxetine clinical trial database found no clinical evidence that concomitant use of combination oral contraceptives (COCs) and fluoxetine affects the safety or efficacy of either agent; these results are consistent with findings in a study of sertraline use in women with PMDD using COCs.³¹

Agents for Ovulation Suppression

Gonadotropin-releasing hormone (GnRH) agonists. These agents (eg, leuprolide acetate) suppress ovarian steroid production,^{32,33} and some studies have found them to be effective for alleviating premenstrual behavioral and physical symptoms^{12,33}; however, these agents are not approved by the FDA for this purpose. GnRH agonists are also not appropriate for long-term use because the hypoestrogenic state they create increases risk of bone loss and osteoporosis.¹

COCs. Although only one of these agents is approved by the FDA for treatment of PMDD, COCs are often prescribed as therapy for premenstrual symptoms. Until recently, few studies had specifically examined the effects of different COC formulations as treatment for PMS. One placebo-controlled 3-cycle trial of a triphasic norethindrone-containing COC found significant reductions in premenstrual breast pain ($p<.05$) and bloating ($p<.01$) from baseline with the COC and none with the placebo; cyclical mood symptoms improved equally in both treatment groups.³⁴ In a 4-cycle study comparing the effects of a triphasic levonorgestrel (LNG)-containing COC and a monophasic LNG-containing COC with a desogestrel (DSG)-containing COC on premenstrual mood symptoms, all treatment groups experienced improvement in symptoms from baseline; however, there were fewer negative cyclical mood changes with the DSG-containing COC than with the LNG-containing formulations.³⁵ In a retrospective study of 658 women who reported their recalled mood responses to use of all types of COCs, 16.3% reported premenstrual mood deterioration while 12.3% reported premenstrual mood improvement and 71.4% reported no change.³⁶ These results suggest that currently available COCs generally do not worsen and may ameliorate PMS mood symptoms.³⁷ Use of extended- and/or continuous-use COC regimens has been suggested to reduce the frequency of ovulatory cycles and thus of PMS symptoms.^{38,39}

Recently, studies of COCs containing drospirenone (DRS), a progestin with antiminerocorticoid and antiandrogenic activity derived from spiro lactone, have found reductions in premenstrual physical and mood symptoms in users of this formulation overall as well as in women diagnosed with PMDD.⁴⁰⁻⁴⁷ In a 6-cycle comparative study of premenstrual symptoms in 50 women using a COC containing 30 mcg ethinyl estradiol (EE)/3 mg DRS and 49 women using a COC containing 30 mcg EE/150 mcg LNG for contraception for 21 days of each 28-day cycle, EE/DRS reduced prevalence of premenstrual physical and mood symptoms to 32% while EE/LNG did not alter the prevalence of premenstrual symptoms (61.2%), a significant ($p=.005$) difference between groups.⁴¹ A large open-label study of premenstrual symptoms in 822 women using DRS/EE 30 mcg for contraception, who were surveyed at baseline and after 2 cycles of COC use, included 589 women self-reported as having PMS.⁴² Improvements from baseline in the total survey population included significant reductions in premenstrual symptoms ($p<.001$) and decreases in symptoms of physical discomfort and/or emotional distress affecting general sense of well-being and ability to perform usual activities ($p<.05$).

Two multicenter, randomized, double-blind, placebo-controlled trials evaluated the effects of a COC containing 20 mcg EE/DRS 3 mg (24 active tablet/4 inactive tablet regimen) in women diagnosed with PMDD according to DSM-IV criteria.^{46,47} In the first study (comprised of 2 run-in and 3 treatment cycles [N=450]) the DRS/EE regimen was associated with a significantly greater 47% reduction from baseline in the total DRSP score than the 38% reduction associated with the placebo.⁴⁶ The median reductions in individual mood and physical symptoms with DRS/EE ranged from 45% to 62%. The second study employed a crossover design consisting of a 2-cycle run-in period, 3 treatment cycles, 1 treatment-free washout cycle, and 3 cycles with the converse treatment.⁴⁷ Total DRSP scores were decreased by 48% from baseline in the DRS/EE group and by 29% in the placebo group in the first treatment period, a significant difference; after

(continued on page 7)

Etonogestrel-Containing Single-Rod Implant: A New Contraceptive Option

Philip D. Darney, MD, MSc, and Daniel R. Mishell, Jr, MD

In July 2006, the United States Food and Drug Administration (FDA) approved a single-rod progestin-only etonogestrel (ENG; active metabolite of desogestrel) subdermal contraceptive for 3 years of use.^{1,2} The implant must be removed by the end of the third year of use and may be replaced with a new implant if continued contraception is desired. The single-rod implant is simpler to insert and remove than the previously available 6-capsule levonorgestrel (LNG) implant.³ Women who wish to consider using implant contraception should benefit from education and counseling by their clinicians.

Description and Pharmacology

The new implant is a 4-cm long, 2-mm diameter rod of ethylene vinylacetate (EVA),² with a nonbiodegradable solid core of 40% EVA and 60% ENG (68 mg).⁴ During the first 2 months of use, ENG is released at the rate of 60 to 70 mcg/day, decreasing to approximately 25 to 30 mcg/day by the end of the third year.^{2,5} Serum levels of ENG above 90 pg/mL are sufficient to suppress ovulation⁶; a mean serum level of ENG 265.9±80.89 pg/mL is achieved 8 hours after insertion.³ After 1 year and 3 years, respectively, ENG mean serum concentrations are 196 pg/mL and 156 pg/mL.^{2,3,7} No accumulation of ENG occurs, as bioavailability remains constant at close to 100% and clearance at about 7.5 L/h.⁵ After implant removal, serum ENG levels become undetectable (<20 pg/mL) within 1 week,³ and ovulation occurs in almost all users within 3 to 6 weeks after removal.^{3,8}

Mechanisms of Action and Efficacy

The major contraceptive mechanism of action of the ENG implant is ovulation inhibition, primarily through suppression of the luteinizing hormone (LH) surge.^{3,8-10} In addition, cervical mucus is thickened, hindering sperm penetration.⁸⁻¹⁰

In 4 large clinical trials conducted in the United States,¹¹ 8 European countries plus Chile,^{12,13} Thailand,¹⁴ and Mexico,¹⁵ no in-treatment pregnancies occurred among 1482 women who used the ENG implant for a total of 2928.6 woman-years. A Pearl Index of 0.38 per 100 woman-years of use, representing 6 pregnancies during 20,648 cycles of use, is reported in product labeling.² Efficacy in obese women has not been studied; women weighing more than 130% of their ideal body weight were not enrolled in the clinical trials.^{2,11}

Safety

In healthy women, the ENG implant has no clinically meaningful effects on lipid metabo-

lism, carbohydrate metabolism, liver function, hemostatic factors, blood pressure, or thyroid or adrenal function.^{11,16-21} ENG is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme.² Therefore, the ENG implant is not recommended for women chronically using hepatic-enzyme inducers, such as some antiepileptic agents, because ENG levels may be substantially reduced.²

An open, prospective study in healthy women aged 18 to 40 (N=76) evaluated the effects of ENG implant use (n=46) on bone mineral density (BMD) compared with copper-bearing intrauterine contraceptive (IUC) use (n=30) over 2 years.²² There were no statistically significant differences in BMD at the lumbar spine, femoral neck, Ward's triangle, trochanter, or distal radius from baseline up to 2 years in either group or between implant users and IUC users.²² Median estradiol serum levels were slightly higher in the implant group than in the IUC group throughout the study.

In the multicenter study, a gradual mean percent increase of 3.5% (0.8±1.59 kg/m²) in body mass index (BMI) was observed over 3 years.^{12,13} In 20.2% of women (128/635) a clinically significant increase from baseline BMI (>10%) was observed at one or more measurements.¹² In US users of the ENG implant (N=330), mean weight gain was 2.8 pounds at 1 year and 3.7 pounds at 2 years of use.² In the comparative bone density study of the ENG implant and a copper IUC, implant users gained a mean 1.9 kg over 2 years of use while IUC users had no change in weight.²²

As with all progestin-only contraceptive methods, alterations in bleeding patterns, primarily bleeding irregularities, are common with ENG implant use. During the first 90 days after insertion in the 3-year multicenter trial, implant users experienced infrequent bleeding (51%), prolonged bleeding (40%), frequent bleeding (11.5%), and amenorrhea (0.9%).^{12,13} However, both normal bleeding patterns and amenorrhea become more common with increasing duration of use.¹² By 2 years of use, the incidence of amenorrhea was 11.9% and of prolonged bleeding 17.8%.¹³ In the 2-year US clinical trial (N=330, 6186 cycles), the most common reason for method discontinuation was bleeding irregularities (13%), including amenorrhea, followed by other adverse experiences (23%; most frequent reasons after bleeding irregularities: emotional lability [6.1%], weight increase [3.3%], depression [2.4%], acne [1.5%]).^{2,11}

Product labeling for the ENG implant states that clinicians must receive instruction and training about correct insertion and removal procedures before ordering the implant.²

Appropriate Users and Counseling

Contraindications to use of the ENG implant in the product labeling are known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; hepatic tumors or active liver disease; undiagnosed abnormal genital bleeding; known or suspected carcinoma of the breast or personal history of breast cancer; and hypersensitivity to any implant components.²

Appropriate candidates for ENG implant use are women who:

- desire long-term, reversible contraception
- have no contraindications to ENG implant use
- cannot or do not wish to use estrogen-containing contraceptives
- are willing to accept bleeding irregularities and/or altered bleeding patterns
- have no objections to the insertion/removal procedures or to palpating the implant when it is in place.

In order for women to make informed decisions about contraceptive selection, and to enhance satisfaction with the chosen method, clinicians should provide anticipatory guidance about various methods suitable for each woman. Counseling about the ENG implant should emphasize this method's advantages, which include high contraceptive efficacy without continued user action, rapid reversibility, long duration of action, and safety. Disadvantages include possible side effects (eg, altered bleeding patterns), the possible sequelae of insertion/removal procedures, and possible lower cost-effectiveness than other methods if use is discontinued before 3 years. Women who are apprehensive about implant use because they have experienced or heard about problems of LNG implant insertion and removal should be provided with information about the simpler ENG implant insertion/removal techniques. Like all other contraceptive methods except condoms, the ENG implant does not provide protection against sexually transmitted infections (STIs); concomitant use of condoms should be recommended to help prevent acquisition of STIs.

REFERENCES

1. US Food and Drug Administration. IMPLANON™ approval letter. Available at: http://www.fda.gov/cder/foi/applletter/2006/021529s000_ltr.pdf. Accessed August 2, 2006.
2. Implanon [package insert]. Roseland, NJ: Organon USA Inc.; 2006.
3. Mäkräinen L, van Beek A, Tuomivaara L, Asplund B, Bennink HC. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. *Fertil Steril*. 1998;69:714-721.
4. Speroff L, Darney PD. Implant contraception. In: *A Clinical Guide for Contraception*. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005: Chapter 5.
5. Wenzl R, van Beek A, Schnabel P, Huber J. Pharmacokinetics of etonogestrel released from the contraceptive implant Implanon®. *Contraception*. 1998;58:283-288.

6. Diaz S, Pavez M, Moo-Young AJ, Bardin CW, Croxatto HB. Clinical trial with 3-keto-desogestrel subdermal implants. *Contraception*. 1991;44:393-408. 7. Croxatto HB. Progestin implants for female contraception. *Contraception*. 2002;65:15-19. 8. Le J, Tsourounis C. Implanon: a critical review. *Ann Pharmacother*. 2001;35:329-336. 9. Croxatto HB. Mechanisms that explain the contraceptive action of progestin implants for women. *Contraception*. 2002;65:21-27. 10. Davies GC, Feng LX, Newton JR, van Beek A, Coelingh-Bennink HJT. Release characteristics, ovarian activity and menstrual bleeding pattern with a single contraceptive implant releasing 3-ketodesogestrel. *Contraception*. 1993;47:251-261. 11. Funk S, Miller MM, Mishell DJ, Jr, et al, for The Implanon™ US Study Group. Safety and efficacy of Implanon™, a single-rod implantable contraceptive containing etonogestrel. *Contraception*. 2005;71:319-326. 12. Croxatto HB. Clinical profile of Implanon®: a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care*. 2000;5(suppl

2):21-28. 13. Croxatto HB, Urbancsek J, Massai R, Bennink HC, van Beek A, and the Implanon® Study Group. A multicentre efficacy and safety study of the single contraceptive implant Implanon®. *Hum Reprod*. 1999;14:976-981. 14. Kiriwatt O, Patanayindee A, Koetsawang S, Korver T, Coelingh Bennink HJT. A 4-year pilot study on the efficacy and safety of Implanon®, a single-rod hormonal contraceptive implant, in healthy women in Thailand. *Eur J Contracept Reprod Health Care*. 1998;3:85-91. 15. Otero Flores JB, Balderas ML, Bonilla MC, Vázquez-Estrada L. Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. *Int J Gynaecol Obstet*. 2005;90:228-233. 16. Mascarenhas L, van Beek A, Coelingh Bennink H, Newton J. Twenty-four month comparison of apolipoproteins A-1, A-II, and B in contraceptive implant users (Norplant® and Implanon®) in Birmingham, United Kingdom. *Contraception*. 1998;58:215-219. 17. Biswas A, Viegas OAC, Coelingh Bennink HJT, Korver T, Ratnam SS. Implanon® contraceptive implants:

effects on carbohydrate metabolism. *Contraception*. 2001;63:137-141. 18. Egberg N, van Beek A, Gunnervik C, et al. Effects on the hemostatic system and liver function in relation to Implanon® and Norplant®: a prospective randomized clinical trial. *Contraception*. 1998;58:93-98. 19. Biswas A, Viegas OAC. Effect of etonogestrel subdermal contraceptive implant (Implanon®) on liver function tests – a randomized comparative study with Norplant® implants. *Contraception*. 2004;70:379-382. 20. Edwards JE, Moore A. Implanon: a review of clinical studies. *Br J Fam Plann*. 1999;24:3-16. 21. Biswas A, Viegas OAC, Coelingh Bennink HJT, Korver T, Ratnam SS. Effect of Implanon® use on selected parameters of thyroid and adrenal function. *Contraception*. 2000;62:247-251. 22. Beerhuizen R, van Beek A, Massai R, Mäkäräinen L, in't Hout J, Coelingh Bennink H. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon® compared to a non-hormonal method of contraception. *Hum Reprod*. 2000;15:118-122.

Contraceptive Use in Women With Premenstrual Disorders (continued from page 5)

crossover, total DRSP scores were decreased by 30% in the DRS/EE group and increased by 19% in the placebo group. As a result of these studies, the FDA recently approved this COC formulation to have an indication for treatment of PMDD in addition to contraception.⁴⁸

Other hormonal methods. No data are available regarding the effects of other combination hormonal contraceptive methods (transdermal patch, vaginal ring) in the treatment of PMS/PMDD and few data are available regarding use of progestin-only methods (depot medroxyprogesterone acetate [DMPA], etonogestrel implant) for these conditions.²⁴ However, the transdermal patch, the vaginal ring, and DMPA inhibit ovulation as effectively as do COCs, and the implant also suppresses ovulation in some users, so some women may experience improvement in some premenstrual symptoms with use of these methods. In a 6-cycle or 13-cycle comparative trial of factors related to contraceptive user satisfaction, users of the transdermal contraceptive patch at last cycle of use reported greater improvement from baseline in premenstrual emotional and physical symptoms than did users of a COC containing 20 mcg EE/150 mcg gestodene (not available in the United States; 35.4% vs 28.6%, respectively, $p < .01$).⁴⁹ Premenstrual symptoms improved with increasing age in the patch group but not in the COC group. A prospective study of mood changes among adolescents found that DMPA users showed significant ($p = .03$) improvement in negative affect over a period of 12 months compared with adolescents using nonhormonal contraception, as measured by the Beck Depression Inventory.⁵⁰

Summary and Conclusions

The premenstrual disorders PMS and PMDD are characterized by somatic and affective symptoms, occurring only in the luteal phase of the menstrual cycle, that interfere with a woman's life. Guidelines developed by ACOG for PMS and APA for PMDD have formalized these diagnostic criteria. Differential diagnosis of premenstrual conditions according to these criteria is best achieved through use of a standardized calendar/history form to document symptoms prospectively over at least 2 to 3 cycles and to identify the timing, recurrence, and pattern of relevant symptoms. A variety of therapeutic agents have been found effective for treating PMS and PMDD, including some COCs. One COC formulation was recently approved by the FDA for treatment of PMDD. To prevent pregnancy in a woman using a nonhormonal therapy for PMS or PMDD, any contraceptive method can be used concomitantly.

REFERENCES

- American College of Obstetricians and Gynecologists. Premenstrual syndrome. *ACOG Practice Bulletin*. 2000;Number 15. 2. Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD) [review]. *Psychoneuroendocrinology*. 2003;28(suppl 3):1-23. 3. Dickerson LM, Mazzyck PJ, Hunter MH. Premenstrual syndrome. *Am Fam Physician*. 2003;67:1743-1752. 4. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. Text revision. Washington, DC: American Psychiatric Association; 2000. 5. Dean BB, Borenstein JE, Knight K, Yonkers K. Evaluating the criteria used for identification of PMS. *J Womens Health (Larchmt)*. 2006;15:546-555. 6. Winer SA, Rapkin AJ. Premenstrual disorders: prevalence, etiology and impact. *J Reprod Med*. 2006;51:339-347. 7. Robinson RL, Swindle RW. Premenstrual symptom severity: impact on social functioning and treatment-seeking behaviors. *J Womens Health Gen Based Med*. 2000; 9:757-768. 8. Ramcharan S, Love EJ, Fick GH, Goldfien A. The epidemiology of premenstrual symptoms in a population-based sample of 2650 urban women: attributable risk and risk factors. *J Clin Epidemiol*. 1992;45:377-392. 9. Campbell EM, Peterkin D, O'Grady K, Sanson-Fisher R. Premenstrual symptoms in general practice patients: prevalence and treatment. *J Reprod Med*. 1997;42:637-646. 10. Wittchen H-U, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the

- community. *Psychol Med*. 2002;32:119-132. 11. Freeman EW. Premenstrual syndrome and premenstrual dysphoric disorder: definitions and diagnosis. *Psychoneuroendocrinology*. 2003;28(suppl 3): 25-37. 12. Halbreich U, O'Brien PMS, Eriksson E, Bäckström T, Yonkers KA, Freeman EW. Are there differential symptom profiles that improve in response to different pharmacological treatments of premenstrual syndrome/premenstrual dysphoric disorder? *CNS Drugs*. 2006;20:523-547. 13. Rapkin AJ, Morgan M, Goldman L, Brann DW, Simone D, Mahesh VB. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol*. 1997;90:709-714. 14. Girdler SS, Straneva PA, Light KC, Pedersen CA, Morrow AL. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biol Psychiatry*. 2001;49:788-797. 15. Steiner M, Lepage P, Dunn EJ. Serotonin and gender-specific psychiatric disorders. *Int J Psychiatry Clin Pract*. 1997;1:3-13. 16. Rapkin AJ, Edelmann E, Chang LC, Reading AE, McGuire MT, Su T-P. Whole-blood serotonin in premenstrual syndrome. *Obstet Gynecol*. 1987;70:533-537. 17. Wihlbäck A-C, Sundström Poromaa I, Bixo M, Allard P, Mjörndal T, Spigset O. Influence of menstrual cycle on platelet serotonin uptake site and serotonin_{2A} receptor binding. *Psychoneuroendocrinology*. 2004;29:757-766. 18. Endicott J, Nee J, Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. *Arch Womens Ment Health*. 2006;9:41-49. 19. Madison Institute of Medicine. Daily Record of Severity of Problems. Available at: <http://www.pmd.factsforhealth.org/have/dayrecord.html>. Accessed September 11, 2006. 20. Hunter MS, Ussher JM, Browne SJ, Cariss M, Jolley R, Katz M. A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. *J Psychosom Obstet Gynaecol*. 2002;23:193-199. 21. Halbreich U. Algorithm for treatment of premenstrual syndromes (PMS): experts' recommendations and limitations [review]. *Gynecol Endocrinol*. 2005;20:48-56. 22. Bertone-Johnson ER, Hankinson SE, Bendich A, Johnson SR, Willett WC, Manson JE. Calcium and vitamin D intake and risk of incident premenstrual syndrome. *Arch Intern Med*. 2005;165:1246-1252. 23. Steiner M, Pearlstein T, Cohen LS, et al. Expert guidelines for the treatment of severe PMS, PMDD, and comorbidities: the role of SSRIs. *J Womens Health (Larchmt)*. 2006;15:57-69. 24. Wyatt K, Dimmock P, Jones P, Obhrai M, O'Brien S. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *Br Med J*. 2001;323:1-8. 25. Sarafem [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2006. 26. Paxil CR [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2006. 27. Zolof [package insert]. New York, NY: Pfizer Inc; 2006. 28. Dimmock PW, Wyatt KM, Jones PW, O'Brien PMS. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet*. 2000;356:1131-1136. 29. Wyatt KM, Dimmock PW, O'Brien PM. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2002;CD001396. 30. Luisi AF, Pawasauskas JE. Treatment of premenstrual dysphoric disorder with selective serotonin reuptake inhibitors. *Pharmacotherapy*. 2003;23:1131-1140. 31. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. *Am J Obstet Gynecol*. 2002;187:551-555. 32. Lauffer MR, Townsend NL, Parsons KE, et al. Inducing amenorrhea during bone marrow transplantation: a pilot study of leuprolide acetate. *J Reprod Med*. 1997;42:537-541. 33. Clinical Trial of Leuprolide Acetate for the Treatment of PMS. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00001259>. Accessed August 9, 2006. 34. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res*. 1992;36:257-266. 35. Bäckström T, Hansson-Malmström Y, Lindhe B-A, Cavalli-Björkman B, Nordenström S. Oral contraceptives in premenstrual syndrome: a randomized comparison of triphasic and monophasic preparations. *Contraception*. 1992;46:253-268. 36. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. *Am J Obstet Gynecol*. 2003;189:1523-1530. 37. Rapkin AJ, Biggio G, Concas A. Oral contraceptives and neuroactive steroids. *Pharmacol Biochem Behav*. 2006;84:628-634. 38. Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. *Obstet Gynecol*. 1997;89:179-183. 39. Sulak PJ. Ovulation suppression of premenstrual symptoms using oral contraceptives. *Am J Manag Care*. 2005;11:S492-S497. 40. Freeman EW, Kroll R, Rapkin A, et al, for the PMS/PMDD Research Group. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gen Based Med*. 2001;10:561-569. 41. Sangthawan M, Taneepanichskul S. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms. *Contraception*. 2005;71:1-7. 42. Borenstein J, Yu H-T, Wade S, Chiou C-F, Rapkin A. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life. *J Reprod Med*. 2003;48:79-85. 43. Foidart J-M, Wuttke W, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care*. 2000;5:124-134. 44. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception*. 2000;61:105-111. 45. Brown C, Ling F, Wan J. A new monophasic oral contraceptive containing drospirenone: effect on premenstrual symptoms. *J Reprod Med*. 2002;47: 14-22. 46. Yonkers KA, Brown C, Pearlstein TB, Foege M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol*. 2005;106:492-501. 47. Pearlstein TB, Bachmann GA, Zacc HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. *Contraception*. 2005;72:414-421. 48. US Food and Drug Administration. FDA approval letter: NDA 21-873. Available at: <http://www.fda.gov/cder/foi/applletter/2006/021873s00LTR.pdf>. Accessed December 1, 2006. 49. Urdl W, Apter D, Alperstein A, et al, for the ORTHO EVRA/EVRA 003 Study Group. Contraceptive efficacy, compliance and beyond: factors related to satisfaction with once-weekly transdermal compared with oral contraception. *Eur J Obstet Gynecol Reprod Biol*. 2005;121: 202-210. 50. Gupta N, O'Brien R, Jacobsen LJ, et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. *J Pediatr Adolesc Gynecol*. 2001;14:71-76.

REFERENCES

1. American College of Obstetricians and Gynecologists. Use of hormonal contraception in women with coexisting medical conditions. ACOG Practice Bulletin number 73. *Obstet Gynecol.* 2006; 107:1453. 2. Rosendaal FR, Van Hylckama Vlieg A, Tanis BC, Helmerhorst FM. Estrogens, progestogens and thrombosis [review]. *J Thromb Haemost.* 2003;1:1371-1380. 3. Gerstman BB, Piper JM, Tomita DK, Ferguson WJ, Stadel BV, Lundin FE. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. *Am J Epidemiol.* 1991;133:32-37. 4. Godland IF, Winkler U, Lidgaard Ø, Crook D. Occlusive vascular diseases in oral contraceptive users: epidemiology, pathology and mechanisms [review]. *Drugs.* 2000;60:721-869. 5. Farmer RDT, Preston TD. The risk of venous thromboembolism associated with low oestrogen oral contraceptives. *J Obstet Gynaecol.* 1995;15:195-200. 6. Cardiovascular disease and steroid hormone contraception. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser.* 1998;877:i-89. 7. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception.* 2006;73:223-228. 8. Petitti DB, Sidney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stroke in users of low-dose oral contraceptives. *N Engl J Med.* 1996;335:8-15. 9. Schwartz SM, Petitti DB, Siscovick DS, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. *Stroke.* 1998;29:2277-2284. 10. Sidney S, Siscovick DS, Petitti DB, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. *Circulation.* 1998;98:1058-1063. 11. Heinemann LAJ. Emerging evidence on oral contraceptives and arterial disease. *Contraception.* 2000; 62:29S-36S. 12. Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med.* 2001;161:1065-1070. 13. Spannagl M, Heinemann LAJ, DoMinh T, Assmann A, Schramm W, Schürmann R. Comparison of incidence/risk of venous thromboembolism (VTE) among selected clinical and hereditary risk markers: a community-based cohort study [review]. *Thromb J.* 2005;3:8. 14. Vandenbroucke JP, Koster T, Briët E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet.* 1994;344:1453-1457. 15. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives: results of an international, multicenter, case-control study. *Contraception.* 1998;57:315-324. 16. Samsioe G. Coagulation and anticoagulation effects of contraceptive steroids. *Am J Obstet Gynecol.* 1994;170 (pt 2):1523-1527. 17. Heinemann LAJ, Assmann A, DoMinh T, Garbe E, and the Transnational Research Group on Oral Contraceptives and the Health of Young Women. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Eur J Contracept Reprod Health Care.* 1999;4:67-73. 18. World Health Organization. *Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use.* 3rd ed. Geneva, Switzerland: World Health Organization; 2004. 19. Kim C, Siscovick DS, Sidney S, Lewis CE, Kiefe CI, Koepsell TD. Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA Study. *Diabetes Care.* 2002;25:1027-1032. 20. Kim C, Seidel KW, Begier EA, Kwok YS. Diabetes and depot medroxyprogesterone contraception in Navajo women. *Arch Intern Med.* 2001;161:1766-1771. 21. Petersen KR, Skouby SO, Sidelmann J, Molsted-Pedersen L, Jespersen J. Effects of contraceptive steroids on cardiovascular risk factors in women with insulin-dependent diabetes mellitus. *Am J Obstet Gynecol.* 1994;171:400-405. 22. Kjos SL. Contraception in diabetic women. *Obstet Gynecol Clin North Am.* 1996;23:243-258. 23. Klein BE, Klein R, Moss SE. Mortality and hormone-related exposures in women with diabetes. *Diabetes Care.* 1999;22:248-252. 24. Kjos SL, Buchanan TA. Postpartum management, lactation, and contraception. In: *Reece EA, Coustan DR, Gabbe SG, eds. Diabetes in Women: Adolescence, Pregnancy, and Menopause.* 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2004:441-449. 25. Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *JAMA.* 1998;280:533-538. 26. Seasonale [package insert]. Pomona, NY: Duramed Pharmaceuticals, Inc.; 2003. 27. ORTHO EVRA [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2006. 28. NuvaRing [package insert]. Roseland, NJ: Organon USA Inc.; 2005. 29. Grigoryan OR, Grodnitskaya EE, Andreeva EN, Shestakova MV,

Melnichenko GA, Dedov II. Contraception in perimenopausal women with diabetes mellitus. *Gynecol Endocrinol.* 2006;22:198-206. 30. Rogovskaya S, Rivera R, Grimes DA, et al. Effect of a levonorgestrel intrauterine system on women with type 1 diabetes: a randomized trial. *Obstet Gynecol.* 2005;105: 811-815. 31. Curtis KM, Mohllajee AP, Martins SL, Peterson HB. Combined oral contraceptive use among women with hypertension: a systematic review. *Contraception.* 2006;73:179-188. 32. Bonnar J. Coagulation effects of oral contraception. *Am J Obstet Gynecol.* 1987;157:1042-1048. 33. Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? A systematic review. *Contraception.* 2006;73:166-178. 34. Ortho Tri-Cyclen Lo [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2004. 35. Middeldorp S, Meinardi JR, Koopman MM, et al. A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. *Ann Intern Med.* 2001;135:322-327. 36. Comp PC. Should coagulation tests be used to determine which oral contraceptive users have an increased risk of thrombophlebitis [commentary]? *Contraception.* 2006;73:4-5. 37. Speroff L, Darney PD. Oral contraception. In: *A Clinical Guide for Contraception.* 4th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2005:21-138. 38. Winkler UH. Blood coagulation and oral contraceptives: a critical review. *Contraception.* 1998;57:203-209. 39. Hellgren M, Svensson PJ, Dahlbäck B. Resistance to activated protein C as a basis for venous thromboembolism associated with pregnancy and oral contraceptives. *Am J Obstet Gynecol.* 1995;173:210-213. 40. Spannagl M, Heinemann LAJ, Schramm W. Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? *Eur J Contracept Reprod Health Care.* 2000;5:105-112. 41. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstet Gynecol.* 2002;99:820-827. 42. Ziemann M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with the Ortho Evra™/Evra™ transdermal system: the analysis of pooled data. *Fertil Steril.* 2002;77(suppl 2):S13-S18. 43. Zhang HF, LaGuardia KD, Creanga DL. Higher body weight and body mass index are not associated with reduced efficacy in Ortho Tri-Cyclen Lo users [abstract]. *Obstet Gynecol.* 2006;107:50S. 44. Laino C. Weight does not appear to affect oral contraceptive efficacy. Available at: <http://www.medscape.com/viewarticle/532302>. Accessed August 15, 2006. 45. Westhoff CL, Anderson FD. Seasonale (30 µg of ethinyl estradiol/150 µg of levonorgestrel) extended-regimen oral contraceptive: efficacy and cycle control by body weight [abstract]. *Contraception.* 2006;74:181-182. Abstract 13. 46. Westhoff C. Higher body weight does not affect NuvaRing®s efficacy. Poster presented at: American College of Obstetricians and Gynecologists 52nd Annual Clinical Meeting; May 1-5, 2005; Philadelphia, Pa. 47. Ortho Tri-Cyclen [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2006. 48. Vessey M, Painter R, Yeates D. Oral contraception and epilepsy: findings in a large cohort study. *Contraception.* 2002;66:77-79. 49. Bounds W, Guillebaud J. Observational series on women using the contraceptive Mirena® concurrently with anti-epileptic and other enzyme-inducing drugs. *J Fam Plann Reprod Health Care.* 2002;28:78-80. 50. Implanon [package insert]. Roseland, NJ: Organon USA Inc.; 2006. 51. O'Brien MD, Gilmour-White SK. Management of epilepsy in women [review]. *Postgrad Med J.* 2005;81:278-285. 52. Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC. Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology.* 1984;34:1255-1258. 53. Petri M, Kim MY, Kalunian KC, et al, for the OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med.* 2005; 353:2550-2558. 54. Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med.* 2005;353:2539-2549. 55. Hernán MA, Hohol MJ, Olek MJ, Spiegelman D, Ascherio A. Oral contraceptives and the incidence of multiple sclerosis. *Neurology.* 2000;55:848-853. 56. Holmqvist P, Wallberg M, Hammar M, Landtblom A-M, Brynhildsen J. Symptoms of multiple sclerosis in women in relation to sex steroid exposure. *Maturitas.* 2006;54:149-153. 57. Legard JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception.* 2006;73:195-204. 58. de Aboud M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera® or Microgynon® on the painful crises of sickle cell anemia patients. *Contraception.* 1997;56:313-316. 59. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. *Am J Obstet Gynecol.* 2002;187:551-555. 60. Westhoff C, Truman C, Kalmuss D, et al. Depressive symptoms and Depo-Provera®. *Contraception.* 1998;57:237-240.

SPONSORING INSTITUTION

The Keck School of Medicine of the University of Southern California is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Keck School of Medicine of the University of Southern California designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity has been planned and produced in accordance with the ACCME Essentials, the Standards for Commercial Support and the Standards for Interpreting the Essentials as applied to CME enduring materials.

In accordance with the ACCME Standards for Commercial Support, the authors for this enduring material have been asked to complete faculty disclosure forms indicating relevant financial relationships. Information is included in the activity material.

The accreditation period for these materials (each issue) is 3 years from the publication date.

ACCREDITING ORGANIZATIONS

This program has been approved for 1 credit per issue in Category 2-B of the American Osteopathic Association CME Program. Upon receipt of documentation of completion from the Keck School of Medicine of the University of Southern California, the individual will be awarded credit.

This program has been approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health for 1.8 contact hours per issue.

Dialogues in Contraception® (Volume 10) has been reviewed and is acceptable for up to 6 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 1/1/06. Term of approval is for 1 year from this date. This issue is approved for 1.5 Prescribed credits. Credit may be claimed for 1 year from the date of this issue.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

Fellows and Junior Fellows of The American College of Obstetricians and Gynecologists may report their participation in this program by sending documentation of completion from the Keck School of Medicine of the University of Southern California.

COOPERATING ORGANIZATIONS

- American Academy of Physician Assistants
- American College of Nurse Practitioners
- American College of Preventive Medicine
- American Medical Women's Association
- Association of Physician Assistants in Obstetrics and Gynecology
- Association of Reproductive Health Professionals
- Association of Women's Health, Obstetric, and Neonatal Nurses
- EngenderHealth
- Healthy Teen Network
- National Association of Nurse Practitioners in Women's Health
- National Family Planning and Reproductive Health Association
- National Medical Association
- Nurse Practitioner Associates for Continuing Education
- Planned Parenthood Federation of America
- Population Council

Produced by



under an unrestricted educational grant from

