



Key issues in women's healthcare

From adolescence through menopause



Adolescent sexual health

by Patricia J. Sulak, MD

Oral contraceptive update

New agents and regimens

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The menopausal transition

How does route of delivery affect the risk/benefit ratio of hormone therapy?

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After menopause

Novel marker helps to identify women at risk for heart disease

by Sandra J. Lewis, MD

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Jointly sponsored by the Dannemiller Memorial Educational Foundation and Dowden Health Media, this educational program is made possible by an unrestricted educational grant from Berlex Laboratories.

Key issues in women's healthcare: From adolescence through menopause

Released: July 2004

Expiration Date for Credit: June 30, 2006

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Statement of Need: Exogenous hormones play an important role in the lives of American women, beginning at puberty and continuing until old age. Oral contraceptives represent the most often used reversible approach to preventing unintended pregnancy in adolescents and adult women; yet, many women are noncompliant. Premenstrual symptoms can have a significant negative impact on a woman's health, quality of life, and productivity throughout her reproductive years. New formulations and regimens provide opportunity to improve compliance. Additionally, physician counseling regarding the health benefits of oral contraceptives can play an important role. Women also need to understand the potential role of exogenous hormones prior to and following menopause, especially the effect of hormones on their risk of heart disease, the most common cause of mortality for American women. To effectively counsel women at each stage of life, physicians need to be able to evaluate the constant deluge of health-based information and misinformation reaching the public and to put it into perspective for their patients.

Intended Audience: This activity is intended for family practice physicians.

Learning Objectives: Upon completion of this activity, the participant should be able to:

- Discuss the role of exogenous hormones throughout the life cycle, including the need for contraception in reproductive-age women and the potential role of hormone therapy in menopausal women
- List the major premenstrual symptoms and common treatment approaches
- Explain the issues of exogenous hormone use during the menopausal transition, including a discussion of high-sensitivity C-reactive protein, a newly identified risk factor for cardiovascular disease
- Explore the importance of personalized counseling for women at these different stages of life

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This publication contains a discussion of unlabeled/investigational use of drugs, as indicated in the text.

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Adolescent sexual health

Patricia J. Sulak, MD

Teenage sexual activity has significant consequences: sexually transmitted diseases (STDs), pregnancy, social and economic disruption, and legal implications. Of the 15 million new cases of STDs that occur each year in the United States, 10 million occur in people aged 15 to 24.¹ Each year, over 400,000 infants are born to teenagers; more than 146,000 are born to those 17 years of age or younger.² In 2000, 18% of reported abortions in the United States were performed on teenagers.³

■ STDs IN ADOLESCENTS

Adolescents aged 10 to 19 years of age are at a higher risk than adults for acquiring STDs because of the likelihood of having multiple and high-risk sexual partners and because adolescents are more susceptible to infection.⁴

Bacterial infections often lead to pelvic inflammatory disease (PID). Although no symptoms may be present initially, the end result may be pelvic pain, infertility, tubal pregnancy, and increased risk of acquiring human immunodeficiency virus (HIV) infection. Viral infections, such as herpes simplex virus (HSV) and HIV, cause severe disease, disability, or fatality in newborns. Significantly, the highest rates of HSV occur with intercourse before age 18 and multiple sexual partners.^{5,6}

Similarly, genital human papillomavirus (HPV) infection, the most common STD, is most common among women who become sexually active in the midadolescent years and have multiple sexual

PRACTICE RECOMMENDATIONS

Adolescents who become sexually active are at greater risk for sexually transmitted diseases than are those who begin sexual activity later in life. While contraceptive strategies can decrease pregnancy and STD acquisition, they have a high failure rate in this age group.

Clinicians should counsel adolescents regarding the importance of delaying sexual activity and the potential hazards of early sexual activity.

partners⁷: 50% to 75% of sexually active women have been infected, and approximately 15% show evidence of current infection. These adolescents often have abnormal Papanicolaou (Pap) smears.⁸ In a study of 80 sexually active adolescents younger than 20 years of age, 90% had HPV evidence in their cervix and 75% in their urine; 38% had abnormal Pap smears. Other STDs were frequent: 15% had chlamydial infection, 6.3% gonorrhea, and 11.3% trichomonal infection.^{9,10} Genital HPV is a precursor for cancer of the vulva, cervix, and anus. One in 4 individuals newly infected with HPV is younger than 22 years.¹¹

■ ADOLESCENTS AND PREGNANCY

Sexually active adolescents account for approximately 10% of all births.¹² The consequences are profound. Children of adolescent mothers are more likely than those of older women to be premature and of low birthweight, have poor health, grow up in a household without a father, run

away from home, be physically abused, and be abandoned or neglected. Daughters are more likely to become teenage mothers; sons are more likely to be imprisoned than are children born to older women. The economic impact has been estimated at \$29 billion per year.¹³

Birth control devices and hormonal formulations are often an ineffective solution in this age-group. Teens have higher pregnancy rates with all birth control methods when compared with adults. Hormonal methods do not protect against STDs. Condoms have a high failure rate for preventing pregnancy, so the rate of failure in protecting against STDs also should be assumed to be high. Additionally, STDs can infect areas of the body not covered by condoms.

■ DELAYING ONSET OF SEXUAL ACTIVITY

Adolescents who are sexually active should be encouraged to seek medical care.

Data suggest that family and school connectedness are associated with delayed onset of sexual activity.¹⁴ Recent surveys by the National Campaign to Prevent Teen Pregnancy revealed that teens regard parents as more influential than friends, religious leaders, teachers, sex educators, the media, and others.¹⁵ These surveys also have consistently shown that most sexually active adolescents wish they had waited to have sex.

Fortunately, fewer teenagers are having sexual intercourse. In a 2001 survey, 42.9% of high-school females reported that they had had intercourse, compared with 50.8% in 1991.¹⁶ The birth rate for teenagers declined 5% between 2001 and 2002, dropping to the lowest level in 60 years.¹²

Healthcare professionals can help their adolescent patients make intelligent decisions to delay sexual activity by talking to their patients, giving accurate information, and becoming involved in providing sex education within their communities

to help adolescents understand that sexual activity is not limited to intercourse (ie, STDs can be spread by a variety of contacts) and to be aware of the long-term risks and consequences of adolescent sexual activity.

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Oral contraceptive update: New agents and regimens

Patricia J. Sulak, MD

For the past 40 years, oral contraceptives (OCs) have been prescribed on a regimen of 21 days of active pills and 7 days of placebo. This schedule was designed to induce a withdrawal bleed and reassure women that they were not pregnant; however, it also meant that women experienced side effects related to menstruation and to OC use. In numerous studies, side effects have been shown to reduce compliance.¹⁻⁵

Over the years, the dosage of estrogen contained in OCs has been decreased. New progestins with improved side-effect profiles have also been introduced, making OC use more tolerable for many women while offering additional benefits that include treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD).

Recently, clinicians also have altered the standard 21/7 regimen, reducing the pill-free interval to eliminate or reduce monthly bleeding as well as the symptoms associated with estrogen withdrawal. These new paradigms also offer the opportunity to improve overall patient health and well-being and reduce menstruation-related gynecologic disorders. They also have raised the question: Is a monthly bleed necessary or desirable? Notably, no health benefits are associated with monthly withdrawal bleeding associated with the 7-day hormone-free interval of OCs. Indeed, until recently, most women did not have frequent monthly bleeds: Menarche generally occurred between ages 16 and 18. Childbearing began at about age 19.5.

PRACTICE RECOMMENDATIONS

Clinicians should counsel patients regarding the potential health benefits and side-effect profile of available OC regimens.

In light of the relation between discontinuation and side effects, clinicians should consider new formulations that reduce common side effects, such as bloating, and are useful in treating PMS and PMDD. New treatment paradigms offer strategies to reduce side effects associated with the hormone-free interval or to reduce frequency of scheduled bleeding. These include reducing the number of pill-free days or extending the menstrual cycle.

Breastfeeding typically lasted for 2 years. Today, women have earlier menarche, postpone pregnancy, limit the number of pregnancies, and breastfeed for a short time. As a result, contemporary women typically experience a greater number of menstrual cycles than did their ancestors.⁶

Contemporary women also often experience menstrual disorders, including menorrhagia, irregular bleeding, dysmenorrhea, PMS, and menstrual migraine headaches. During the perimenopausal transition, they also experience the bleeding irregularities and other symptoms that result from erratic ovulation and hormonal fluctuations.⁷⁻¹²

Conditions treated with OCs The persistent ovulation experienced by many women is assoc-

iated with conditions often treated by OC use,* including: **Abnormal or excessive bleeding patterns.** The effect of OCs on abnormal bleeding patterns was evaluated in a multicenter, randomized, double-blind study of 201 women with dysfunctional uterine bleeding. The study reported significant ($P<.001$) improvement with treatment (ethinyl estradiol [EE]/triphasic norgestimate) compared with placebo.⁸ **Anemia.** The duration of menstrual bleeding and iron stores were evaluated in a study of 268 OC users and nonusers. Use of OCs led to significantly shorter duration of menstrual bleeding and mean serum ferritin levels of 40 mg/L.¹³

Endometriosis. Oral contraceptives have long been used as first-line therapy for endometriosis: the progesterone effect results in atrophy of the endometrium and endometriotic tissue. This effect is also associated with reduced likelihood of new lesions.

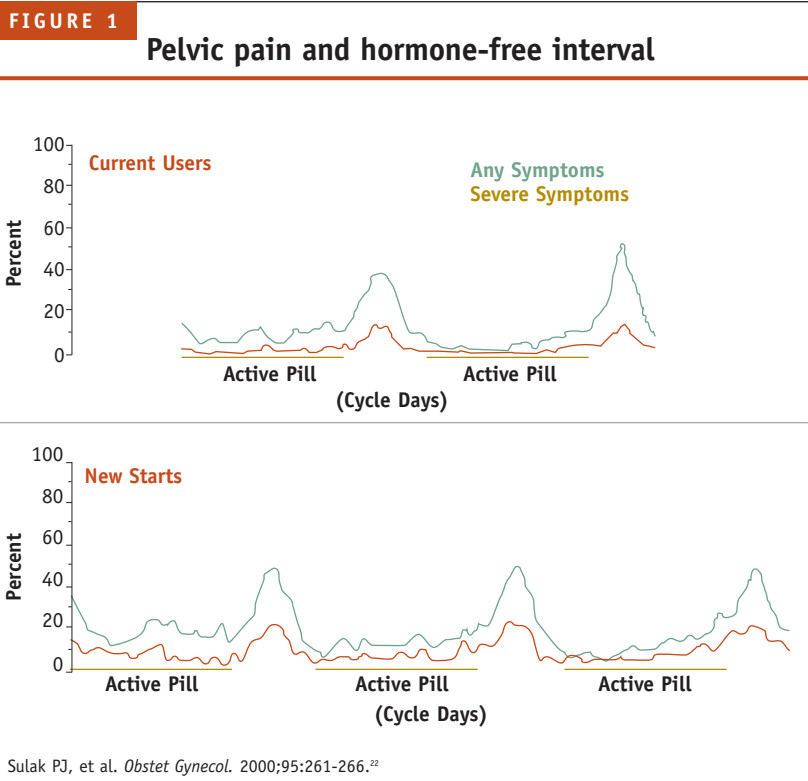
Functional ovarian cysts. In a study enrolling 428 women aged 14 to 45, ovarian cysts were revealed in 29 women. Prevalence was lower for

**This section includes discussions of off-label usage.*

TABLE 1
Hormone Withdrawal Symptoms in Oral Contraceptive Users

	21 active	7 hormone-free	P value
Pelvic pain	21%	70%	<.001
Headaches	53%	70%	<.001
Breast tenderness	19%	58%	<.001
Bloating/swelling	16%	38%	<.001
Use of pain meds	43%	69%	<.001

Sulak PJ, et al. *Obstet Gynecol.* 2000;95:261-266.²²



women using OCs (relative risk = 0.22; confidence interval, 0.13-0.39) than for women using no contraception or nonhormonal intrauterine contraceptive devices.¹⁴

Ovarian cancer. Reduction in ovarian and endometrial cancer risk in women who use OCs has been noted in pivotal clinical trials conducted over the past 3 decades.¹⁵⁻¹⁷ Protection gradually increases within 1 year of initiation of OC use and persists for years after discontinuation.¹⁸

Additionally, OCs provide beneficial effects on menstruation, including reduction in dysmenorrhea^{19,20} improved cycle control, and the emergence of predictable bleeding patterns.^{8,11,21}

■ MENSTRUAL SYMPTOMS AND OC USE

For women using OCs, menstrual symptoms have been shown to be most severe during the traditional 7-day, hormone-free interval. For this reason, clinicians have sought to shorten this interval and reduce symptom severity.* Patterns of hormone withdrawal symptoms in new and long-term OC users were evaluated in a 2000 study by

**This section includes discussions of off-label usage.*

Sulak et al. Of 262 women enrolled in the study, 193 had used OCs for 12 months or longer, 43 were prior users, and 26 had no prior OC use. Participants recorded their symptoms in daily diaries. Symptoms included pelvic pain, headaches, breast tenderness, bloating/swelling, and use of pain medications. Among current OC users, symptoms occurred more frequently during hormone-free intervals than during the 3 active-pill weeks (Table 1). New OC users experienced similar symptom patterns after the first cycle, particularly with respect to pelvic pain (Figure 1) and bloating/swelling (Figure 2).²²

The initiation of some symptoms during the last week of active-pill administration is not surprising: Investigations have shown that some women actually cycle while taking OCs on the traditional 21/7 regimen. Follicle-stimulating hormone levels begin to increase on day 3 to 4 of the pill-free interval, allowing follicular recruitment and estradiol production. Administration of active pills results in follicular degeneration; estrogen withdrawal begins before the next hormone-free interval. In a study comparing 58 women on 21/7 and 24/4 regimens, ovulation was inhibited in all of the cycles in women on the 24/4 regimen and in 74 of 75 cycles of women on the 21/7 regimen. No unruptured follicles were seen in the 24/4 group, whereas 6 were noted in the 21/7 group.²³ Shortening the hormone-free interval from 7 days to 4 days provided greater ovarian suppression in this study.

■ **CHANGING THE STANDARD 21/7 REGIMEN: CURRENT/FUTURE TRENDS**

Shortening the standard pill-free interval provides greater ovarian suppression and decreases the incidence and

severity of hormone withdrawal symptoms.

Shortening the pill-free interval and/or extending the number of active pills improves symptom control and improves contraception. In one study, 292 patients on OC regimens containing EE (30 to 35 µg) and a variety of progestins (norethindrone, levonorgestrel, norgestimate, or desogestrel) were given the option of extending their active pills. Many cited symptoms associated with the hormone-free week as a key reason for doing so. The typical pill-free interval was decreased from 7 days to a median of 5 days; 46% of participants used an interval of less than 7 days. Participants also extended active treatment of an average of 12 weeks of active pills. Of the 92% who attempted an extended regimen, 47% were still on the extended regimen 5 years later.²⁴

An extended-regimen OC has recently been approved. While this regimen extends the time between the pill-free intervals, it is associated with an increased risk of breakthrough bleeding, primarily limited to spotting in the first 2 cycles (each cycle consisting of 84 days of active-pill

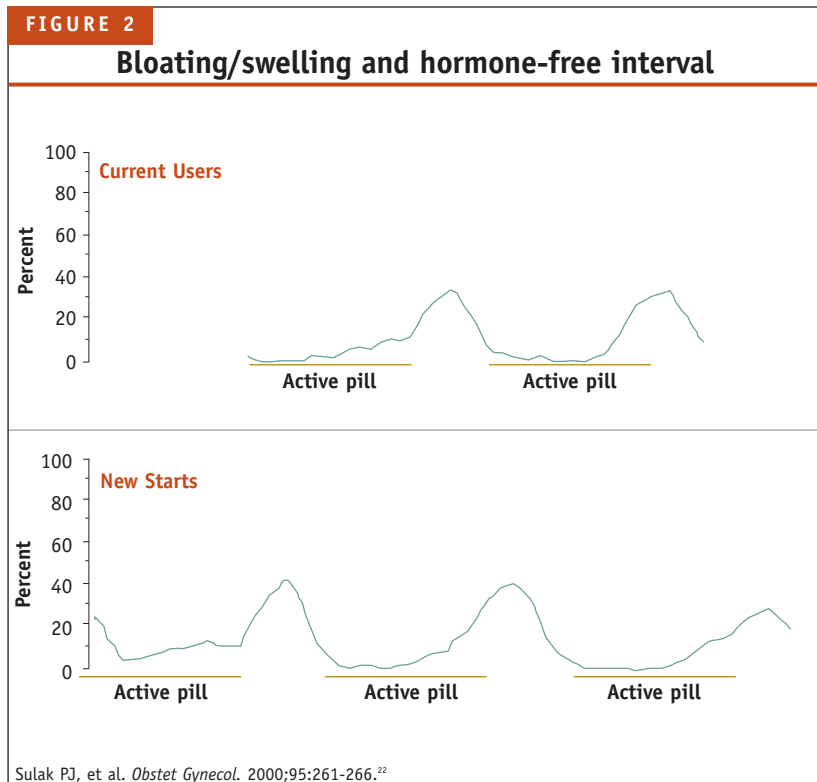


TABLE 2

Pharmacologic Profiles of Progesterone and Synthetic Progestins

Progesterone/progestins	Progestogenic	Antiandrogenic	Antimineralocorticoid	Androgenic
Progesterone	+	(+)	+	-
Drospirenone	+	+	+	-
Norgestimate*	+	-	-	(+)
Levonorgestrel	+	-	-	(+)
Desogestrel	+	-	-	(+)
Norethindrone	+	-	-	(+)
Cyproterone acetate	+	+	-	-

*Metabolized to levonorgestrel 3-oxime and levonorgestrel.
+, distinct effect; (+), negligible effect at therapeutic doses; -, no effect.

administration). Nevertheless, the option of using an OC with a shortened hormone-free interval does allow for flexibility in meeting the needs and desires of individual patients. Specifically, the extended-regimen OCs reduce troublesome menstrual symptoms, thereby improving quality of life (QOL) for women.²⁵

NEW PROGESTINS AND IMPROVED SIDE-EFFECT PROFILES

While progestins are often referred to by generation, these categories relate primarily to their introduction to the market as derivatives of 19-nortestosterone; therefore, they have a mild androgenic effect.²⁶⁻²⁹ The newer progestins were developed to maintain the benefits of low-dose OCs while improving their side-effect profile. Oral contraceptives containing desogestrel and norgestimate, among the so-called "third generation" OCs, provide cycle control comparable to that of earlier low-dose OCs containing levonorgestrel. These formulations have a negligible effect on carbohydrate metabolism and a lower level of androgenicity than formulations containing levonorgestrel.³⁰

The newest progestin on the US market, drospirenone (DRSP), is not derived from 19-nortestosterone. Rather, it is an analogue of spironolactone and, as a result, exhibits antiandrogenic and antimineralocorticoid activity.

Drospirenone shows effects similar to those of endogenous progesterone: potent progestogenic, antiandrogenic, and antimineralocorticoid activities, and no androgenic activity.³¹⁻³⁴ Table 2 shows the biologic activity of progestins.

The OC containing DRSP also provides cycle control comparable to that of other low-dose OCs and has a small impact on carbohydrate metabolism, equal to that of a low-dose OC containing desogestrel.

PROPERTIES OF PROGESTINS AND POTENTIAL BENEFITS

The properties of various progestins offer additional opportunities for the clinician to tailor the choice of an OC to the individual needs of the patient.

Improved acne

While acne generally constitutes a nuisance condition, patient awareness of potential benefits to skin may help improve compliance. Oral contraceptives that contain estrogen should improve acne.³⁰ Currently, 1 EE/norgestimate formulation and 1 EE/norethindrone acetate formulation have approval of the US Food and Drug Administration as treatments for acne.^{35,36} In other countries, an EE/cyproterone acetate (CPA) (an antiandrogenic progestin) formulation is approved for acne.

The EE/DRSP OC has been shown to be as effective as EE/CPA in treating acne.^{37*} In a multi-center, single-blind, randomized study of 125 women, 82 were prescribed DRSP, 3 mg, and EE, 30 µg, while 43 received CPA, 2 mg, and EE, 35 µg. After 9 treatment cycles, the median total acne lesion count was reduced by 62.5% in the EE/DRSP group and 58.8% in the EE/CPA group.³⁸ A study accepted for publication in *Cutis* compared EE/DRSP with EE/norgestimate. The EE/DRSP regimen showed a greater effect in reducing total lesion count (-3.3% [95% CI, -6.5

to -0.1; $P = .02$) and an increased therapeutic effect on facial acne (+3.6% [95% CI, 0.8 to 6.3, $P = .006$]) by cycle 6.³⁹

Improvement of bloating symptoms

Ethinyl estradiol causes an increase in serum aldosterone levels, resulting in sodium and water retention, bloating, and breast tenderness. Drospirenone—the only progestin not derived from 19-nortestosterone—blocks aldosterone at its receptor. As a result, it has diureticlike effects: sodium and water excretion is increased, and potassium may be retained. Thus, the weight gain associated with water retention, common with 19-nortestosterone derivatives, does not occur.⁴⁰

Weight change was monitored in a 26-cycle open-label efficacy study of 887 women who were randomized to DRSP, 3 mg, plus EE, 30 µg, or to desogestrel, 150 µg, plus EE, 30 µg. The EE/desogestrel regimen was associated with a small weight gain over cycles 6 to 26, with a mean range of +0.02 kg to +0.89 kg. The mean weight change of women in the group using DRSP/EE was slightly below the baseline weight for 24 of 26 cycles (range -0.01 kg to -0.15 kg).³⁶

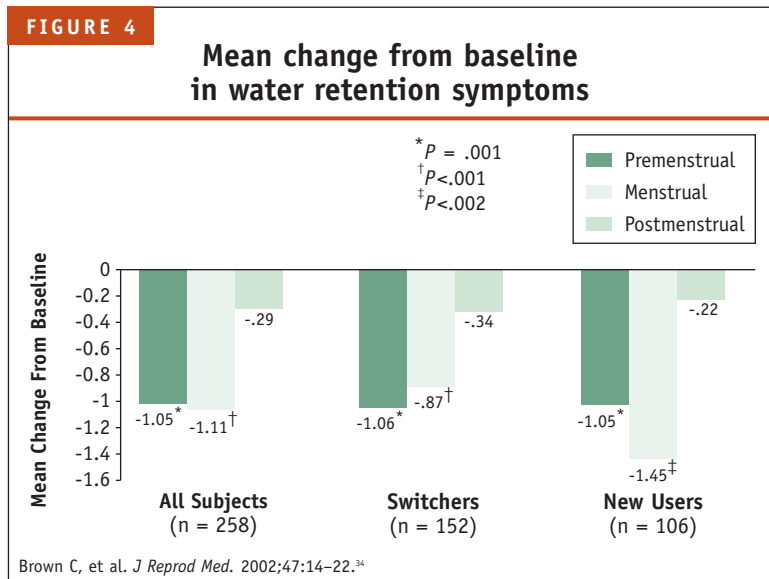
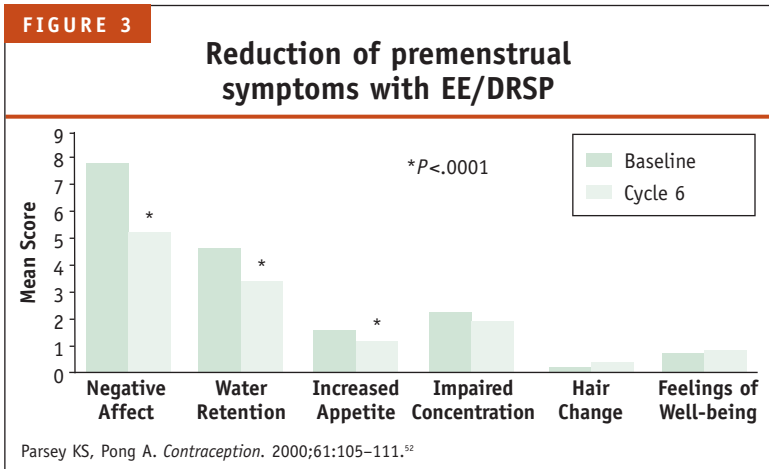
PMS AND PMDD: TREATMENT WITH OCs

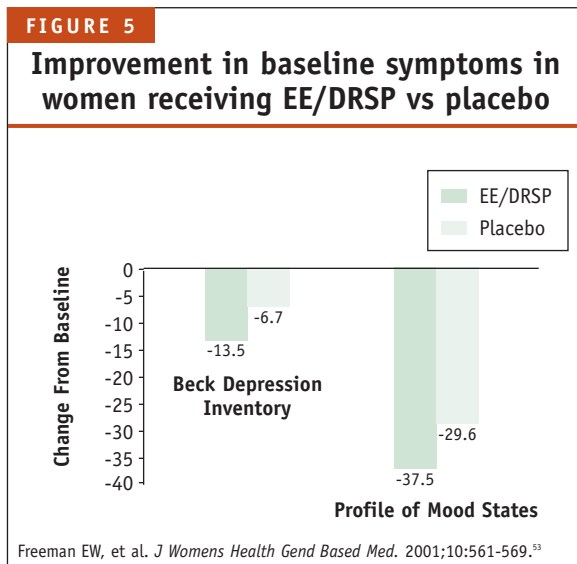
Approximately 70% to 90% of reproductive-age women report some symptoms associated with their menstrual period. Of this group, 20% to 40% believe they have PMS. About 3% to 8% of reproductive-age women have symptoms that are severe enough to qualify as PMDD.⁴¹

In 2000, the American College of Obstetricians and Gynecologists published diagnostic criteria for PMS. One or more of the

following affective and/or somatic symptoms must occur during the 5 days before menses in 3 consecutive prior menstrual cycles: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal, breast tenderness, abdominal bloating, headache, and swelling of extremities. Symptoms must impair some aspect of life.⁴²

While data regarding the use of OCs to treat menstruation-related mood disorders and/or improve QOL are inconsistent, mounting evidence suggests that OCs containing DRSP may provide benefits. Additionally, 1 OC containing a 19-nortestosterone-derived progestin has been asso-





ciated with improved QOL. However, data do not support the use of OCs containing progestins derived from 19-nortestosterone to treat mood disorders.⁴³⁻⁴⁶

Improvement in QOL with OC use

Overall QOL scores have been improved in women receiving OCs containing desogestrel and EE. The Quality of Life and Enjoyment questionnaire was used to assess 614 first-time OC users. Over 4 months, 56% of women noted improved QOL, 18% had no change, and 26% experienced deterioration.⁴⁷ A multicenter observational study enrolling 3679 first-time OC users also revealed statistically significant ($P < .001$) improvements from baseline in physical health, mood, work/school, household activities, social relationships, family relationships, leisure-time activities, daily life, sex life, living situation, vision, general well-being, and overall satisfaction.⁴⁸

Improvement in PMS/PMDD with OC use

More specific improvements to PMDD and PMS symptoms have been associated with DRSP. Several small, randomized, double-blind placebo trials have shown the efficacy of spironolactone in reducing premenstrual and mood symptoms.⁴⁹⁻⁵¹ As noted, DRSP is an analogue of spironolactone.

Trials also have evaluated DRSP efficacy in

treating PMS and PMDD and improving QOL.

In an open-label study lasting 13 cycles, 326 women were evaluated using the Menstrual Distress Questionnaire to record symptoms associated with each phase of the cycle. Effects were recorded at the end of cycle 6. The women who were prescribed EE/DRSP had statistically significant decreases from baseline in negative affect and water retention in all menstrual phases (Figure 3). Increased appetite was significantly lower in the premenstrual and menstrual phases of the cycle.⁵²

A more detailed evaluation of data from this study compared women who were new users ($n = 150$) with those who had switched to EE/DRSP from another OC ($n = 176$). It showed statistically significant symptom improvement within both groups; DRSP minimized negative affect, water retention, and increased appetite in women who switched to EE/DRSP from another OC and in new OC users (Figure 4).³⁴

A randomized, double-blind, placebo controlled trial enrolled 82 participants with PMDD (as defined by the American Psychiatric Association criteria) who received either EE/DRSP or placebo. The primary study endpoint was a change from baseline symptoms reported during the luteal phase of the menstrual cycle using the Calendar of Premenstrual Experiences scale. Secondary endpoints were the Beck Depression Inventory and Profile of Mood States. Women in the active treatment group demonstrated a 14% improvement of symptoms, which indicated a consistent trend in the reduction of symptoms although the improvement was not statistically significant. Differences between the groups reached statistical significance ($P = .027$) for appetite, acne, and food cravings (Figure 5).⁵³

Other studies show a benefit of EE/DRSP on premenstrual symptoms. A survey of 858 women who had recently initiated use of an OC containing DRSP revealed that, after 2 cycles, the women experienced significantly reduced premenstrual symptoms ($P = .000$) and an improved sense of well-being ($P < .05$) compared with baseline. Additionally, in the health-related QOL assess-

ment, statistically significant improvements in the Mental Component Summary ($P = .000$) were observed; improvements in the Physical Component Summary did not reach statistical significance.⁵⁴

In 2003, a 6-cycle open study of EE/DRSP enrolled 336 women to evaluate fluid-related symptoms and general well-being. Participants experienced a significantly reduced incidence and severity of abdominal bloating ($P < .001$) and breast tension ($P < .001$) associated with the menstrual cycle. A beneficial effect also was seen in general well-being ($P < .0001$), as measured by the Psychological General Well-Being Index. The improvement was shown at cycle 3 and maintained at cycle 6.⁵⁵

CONCLUSION

Oral contraceptives offer an excellent strategy to avoid pregnancy and manage or prevent health problems for reproductive-age women. Long-term OC use can also reduce the risk for future gynecologic and other health problems. New regimens that shorten the traditional 7-day hormone-free interval offer opportunities to improve contraceptive efficacy and reduce side effects associated with hormone withdrawal while maintaining the reassurance of monthly bleeding. Other strategies include extending the cycle of active-pill administration beyond the traditional 21 days.

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The menopausal transition

How does route of delivery affect the risk/benefit ratio of hormone therapy?

Lee P. Shulman, MD

A variety of well-respected observational and randomized clinical trials have shown that hormone therapy (HT) effectively treats and prevents menopausal symptoms and osteoporosis.¹⁻⁴ Controversial issues concerning additional potential risks and benefits of HT have received much attention in the medical literature and the lay press, particularly as a result of the reports from the Women's Health Initiative (WHI).⁵

■ THE WHI: WHAT DOES IT MEAN TO YOUR PATIENTS?

The findings from the WHI are, in many ways, consistent with earlier observational studies, which reported increased risks of venous thromboembolic (VTE) events, breast cancer, and stroke with HT use and decreased risks for hip fracture and colon cancer. The WHI and earlier observational trials do differ in 2 important respects: the WHI showed increased risk of coronary heart disease (CHD) among hormone users in the first year of use and increased risk for dementia. Conversely, a large cohort study published in 2003 reported that dementia was diminished with estrogen administration.⁶

Are the WHI findings relevant to clinical practice? Clinicians should note that the WHI findings, while important, may not correlate to the patient population using HT for the relief of menopausal symptoms. The WHI was designed to validate the use of HT in preventing CHD, as had been suggested by

PRACTICE RECOMMENDATIONS

Despite concerns about the risks of HT, relief of menopausal symptoms is an important goal. Clearly, HT remains an important option to improve the quality of life for menopausal women.

Administration should be at the lowest possible dosage and for the shortest duration required to provide symptom relief.

Route of HT administration also should be considered. Nonoral formulations typically administer lower doses than do oral products and provide dosing over extended periods of time, avoiding the peak-to-trough fluctuations associated with daily oral administration.

observational studies. Hence, the primary endpoint was CHD (defined as acute myocardial infarction [MI], silent MI determined from serial electrocardiograms, or CHD death). Hip fracture was the secondary outcome, and invasive breast cancer a primary adverse outcome. Other cardiovascular disease (CVD), fractures, and cancers were also evaluated.

The study population was limited to women aged 50 to 79 years who were, thus, significantly older than the normal population of women who use HT to alleviate hot flashes, sleep disturbances, sexual dysfunction, urinary symptoms, and vaginal atrophy. Indeed, study participants were not experiencing menopausal symptoms.

This group was selected specifically to meet the study design: to assess the impact of HT on CVD in an at-risk population. The use of a symptomatic cohort would have precluded successful randomization and blinding of the study groups. Accordingly, the protocol of the WHI hormone studies precluded the inclusion of symptomatic menopausal women. Therefore, the WHI outcome data may not necessarily be relevant to the care and management of symptomatic menopausal women.

The study had significant limitations in assessing risks and benefits: The impact of HT on quality of life was not assessed, although most women take HT specifically for relief of menopausal symptoms.

Still, in the aftermath of the WHI, physicians are often asked to discuss with patients the key health issues—regarding both risks and benefits—associated with HT. The key results, and their implications for physicians in practice, are described below.

Osteoporosis. After menopause, low estrogen levels lead to an imbalance in bone metabolism; the rate of bone resorption increases, and bone mineral density (BMD) and bone strength decrease. Spinal or hip fractures often occur in the absence of trauma. While calcium and vitamin D supplements and exercise may retard bone resorption, they have not been shown to significantly reduce osteoporosis or fractures.

In numerous studies, bisphosphonates and raloxifene have demonstrated fracture prevention in women with evidence of osteoporosis. However, only bisphosphonates have been shown to prevent hip fracture in women with preexisting osteoporosis. No data show that these agents reduce fracture in women who do not yet have osteoporosis.

The HT arm of the WHI showed a significant reduction in hip fracture in a population not previously diagnosed with osteoporosis. At the end of year 3, BMD had increased by 3.7% in the HT group and 0.14% in the placebo group ($P < .001$). At the end of 5.6 years, 8.6% ($n = 733$) of patients receiving HT experienced a fracture, compared with 11% ($n = 896$) in the placebo group. Cumulatively, HT reduced the risk of fracture by

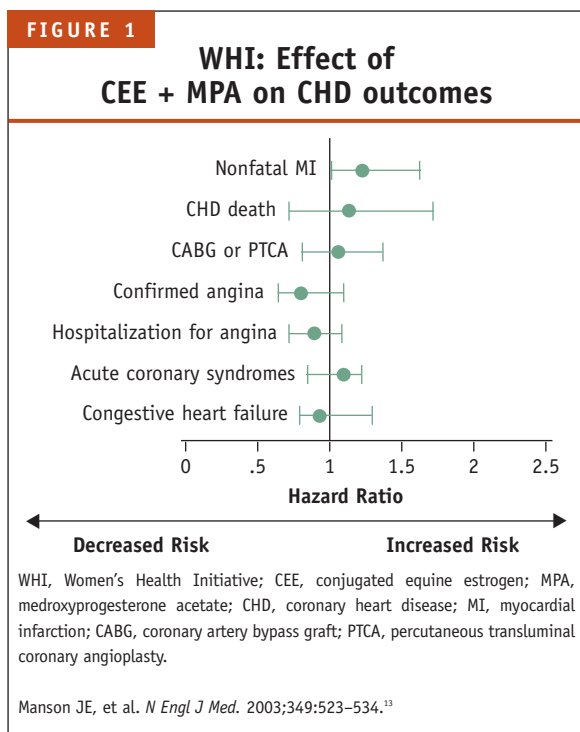
33% in a population already at risk for fracture (44% of the WHI subjects were older than 65 years). While these findings are compelling, they do not justify using HT in a population not experiencing menopausal symptoms.

Breast cancer. The WHI findings were consistent with observational data from earlier studies. At 5.6 years, there were 245 reported cases of breast cancer in the HT group and 185 in the placebo group ($P < .001$). Breast cancer characteristics seen in the 2 groups were different: In the HT group, invasive breast cancers were larger, more likely to be node positive, and at a more advanced stage than were tumors diagnosed in the placebo group.

In contrast, observational data showed a greater likelihood of localized disease in estrogen-users with cancer. In these reports, the risk of breast cancer diagnosis was shown to increase with duration of HT use in current users. This effect was reduced after HT cessation and returned to baseline in about 5 years.⁷⁻¹² Of interest, the estrogen-alone arm of the WHI has not shown the same effect on breast cancer risk as was seen in the combination-HT arm.

Cardiovascular disease. In the WHI, oral HT was associated with a 24% higher rate of nonfatal MI and death from CHD. This was caused primarily by a 28% higher rate of nonfatal MI during year 1 in HT users compared with placebo; the small increases in years 2 through 5 were not statistically significant. The rate of CHD death did not increase significantly. Use of HT did not affect the rate of revascularization procedures, acute coronary syndromes, or congestive heart failure. It did, however, show a trend for reduced rates of confirmed angina and hospitalizations for angina (**Figure 1**).¹³

Additionally, the WHI demonstrated that risk for CHD was significantly greater among women who were more than 20 years postmenopause. **WHI estrogen-only arm.** Fortunately, the recently released results of the estrogen-only arm (discontinued in February 2004) revealed no increase in CHD compared with placebo. The investigators noted that estrogen alone did not appear to increase or decrease the incidence of heart dis-



ease. Administration of estrogen, however, was associated with an increased risk of stroke similar to that observed in the estrogen/progestin study arm (discontinued in 2002). No increase in breast cancer was seen. A decrease in fracture was also observed.¹⁴

CARDIOVASCULAR DISEASE RISK FACTORS, MENOPAUSE, AND HT

In assessing risk of CVD in menopausal women, many factors come into play. Traditional risk factors for CHD include older age, dyslipidemia, family history of premature CHD, diabetes, hypertension, obesity, and a sedentary lifestyle. However, recent experimental and clinical evidence suggests that other independent factors may increase CHD risk, among them C-reactive protein (CRP) and other inflammatory markers, various lipid fractions, thrombogenic and hemostatic factors, homocysteine, and insulin resistance.¹⁵

Menopause is associated with deleterious lipid changes. In a study of 542 healthy premenopausal and postmenopausal women, postmenopausal women had significantly higher levels of total cholesterol, low-density lipoprotein

cholesterol (LDL-C), and triglycerides (TG), and a significantly lower level of high-density lipoprotein cholesterol (HDL-C). These differences were independent of age, body-mass index, or other potentially confounding factors.¹⁶ In this light, the route of administration of HT, as well as the dosage and the type of progestin used, may be of significance.

The Nurses' Health Study, which enrolled 70,533 postmenopausal women and was conducted from 1976 to 1996, showed that the relative risk for stroke was associated with dosage of HT, ranging from a high of 1.63 (95% confidence interval [CI], 1.18-2.26) for conjugated equine estrogen (CEE) dosages equal to or higher than 1.25 mg, and declining to 0.54 (95% CI, 0.28-1.06) for 0.3 mg of CEE.¹⁷

The lipid effects associated with HT were evaluated in a meta-analysis of prospective studies published between 1974 and 2000.¹⁸ A total of 248 studies yielded information on the effects of 42 different HT regimens. The author noted that oral and transdermal regimens—consisting of either estrogen-only or estrogen/progestin formulations—each reduced total LDL-C and raised HDL-C.

Oral HT increased TG levels—estrogen alone more so than estrogen/progestin. The elevations in TG associated with oral administration were lessened by the addition of a progestin. Estrogen-induced lipid changes were opposed according to type of progestogen, with dydrogesterone and medrogestone having the least effect, followed by progesterone, cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate.

Transdermal formulations lowered TG levels whether or not a progestin was administered. Tibolone decreased HDL-C and TG levels. Raloxifene reduced LDL-C levels.

A recent study enrolled 845 healthy postmenopausal women with or without menopausal symptoms. Participants were randomized to receive either transdermal estradiol (E2), 0.045 mg/d plus levonorgestrel 0.015 mg/d, or transdermal unopposed E2, 0.045 mg/d. Transdermal patches were applied once weekly for 13 28-day

cycles. Mean baseline lipid levels were recorded. At the end of the study (Figure 2), transdermal administration of combined therapy (E2, 0.045 mg/d alone with levonorgestrel, 0.015 mg/d) was associated with significant reductions in total cholesterol, LDL-C, and TG levels, and minor reductions in HDL levels. Unopposed E2 resulted in smaller reductions in total cholesterol and LDL-C, with small and insignificant increases in HDL and TG levels. Both regimens controlled the vasomotor symptoms well.¹⁹

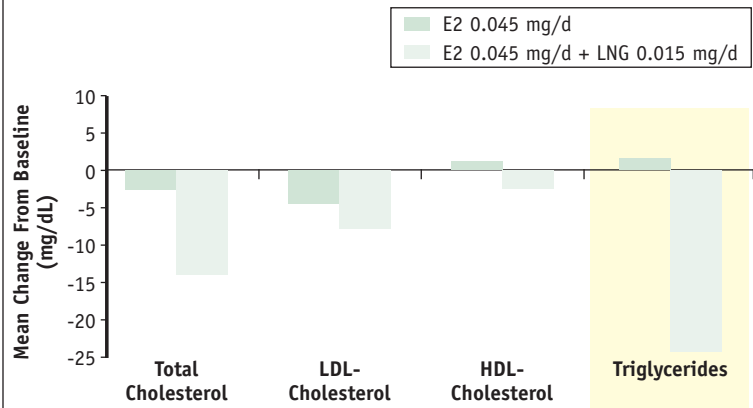
Additionally, oral and transdermal HT have shown different effects on coagulation factors, although limited investigations conducted to date make it difficult to draw useful conclusions for clinicians.¹⁸ New findings regarding CRP are described in detail in "After Menopause: Novel Marker Helps to Identify Women at Risk for Heart Disease," by Sandra J. Lewis, MD, on page S18.

VTE, HT, AND ROUTE OF ADMINISTRATION

In the WHI, the risk for VTE in women who received oral HT was 2.1 times higher than that seen in the placebo group. Pulmonary embolism accounted for one third of serious adverse events in healthy women using supplemental estrogen.²⁰

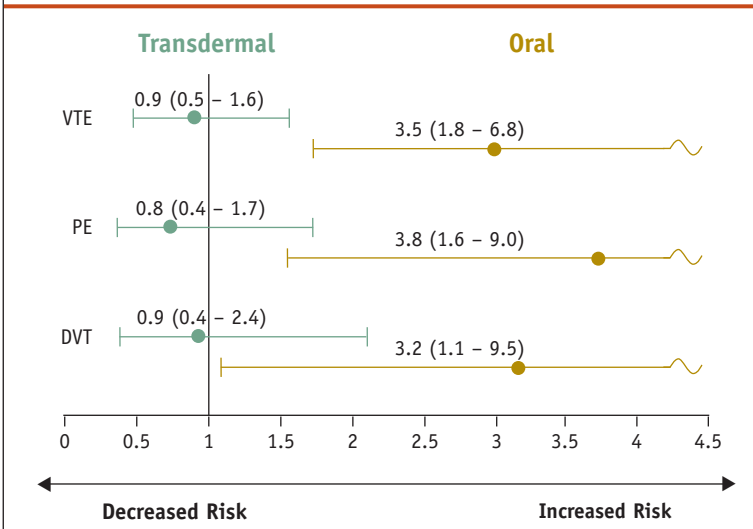
A recent case-control study evaluated the VTE risk for women using oral vs transdermal estrogen in 155 postmenopausal women who had a documented first episode of idiopathic VTE and in 381 controls (Figure 3). After adjustment for confounding factors, the women using oral estrogen had 3.5 times the

FIGURE 2 Effect of continuous once-weekly estradiol plus levonorgestrel transdermal system on lipid levels in healthy postmenopausal women



E2, estradiol; LNG, levonorgestrel; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Shulman LP, et al. *Menopause*. 2002;9:195-207.¹⁹

FIGURE 3 VTE risk with transdermal and oral estrogen



VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep-vein thrombosis. Scarabin PY, et al. *Lancet*. 2003; 362: 428-432.²¹

risk of VTE, 3.8 times the risk for pulmonary embolism, and 3.2 times the risk for deep-vein thrombosis when compared with controls. Transdermal users had no increased risk in any

category.²¹ This finding suggests that it may be possible to greatly improve the risk-benefit profile of HT by selecting a nonoral route of administration.

CONCLUSION

When treating women for menopausal symptoms, clinicians should put the findings of the WHI into perspective. The patient's overall risk profile and the severity of menopausal symptoms should be evaluated. The beneficial effects of HT on bone health and risk reduction for colorectal cancer should not be casually dismissed. Additionally, the selection of a nonoral or low-dose product may provide an efficacious treatment with a lower risk profile.

The basic question is: Why is HT being prescribed? For several years, most physicians prescribed HT to prevent heart disease and treat vasomotor symptoms or osteoporosis. The WHI has shown that HT should not be prescribed to prevent heart disease. Hormone therapy represents an appropriate treatment of osteoporosis after other medications with potentially less serious outcomes have failed. Studies have not shown that pharmacologic treatment of women with osteopenia or family history of osteoporosis is indicated.

If HT is of potential value to the patient for the relief of menopausal symptoms or for the prevention or treatment of osteoporosis, the potential impact of routes of administration should be considered. Further study may answer the question regarding potential effects of transdermal vs oral administration. It is possible that future investigations will show that HT applied transdermally does not produce the cardiovascular events that were shown in the WHI.

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After menopause

Novel marker helps to identify women at risk for heart disease

Sandra J. Lewis, MD

At menopause, a woman's risk of cardiovascular disease (CVD) begins to increase. The prevalence of coronary heart disease (CHD) increases from 5.5% in women aged 45 to 54, to 8.4% in women aged 55 to 64, to 11.1% in women aged 65 to 74, and to 16.1% in women aged 75 and older.¹ Approximately 52 million women will reach the menopausal transition during the next 10 years; half will live more than one third of their lives postmenopause. Since CVD represents the greatest health risk for postmenopausal women, this life-stage is an ideal time for clinicians to review CVD risk and develop strategies to prevent or manage risk factors.

In this light, a novel marker for CVD, high-sensitivity C-reactive protein (hs-CRP), may provide a useful tool to help clinicians assess risk, particularly in patients at intermediate or incremental risks by traditional risk-factor assessment of hypertension, hyperlipidemia, smoking, obesity, diabetes, sedentary lifestyle, and a family history of early heart disease. While treatment guidelines for high- and low-risk patients are clearly defined, clinicians face challenges in determining the optimum treatment for patients at intermediate risk. For this population, the additional information provided by assessing hs-CRP levels can help physicians make the most appropriate management decision for each patient. Strategies to reduce elevated CRP levels also should be considered, including lifestyle changes (exercise, weight

PRACTICE RECOMMENDATIONS

Global cardiovascular risk should be assessed for all patients.

Measurement of hs-CRP independently predicts CHD risk. It enhances CHD risk assessment, especially in patients with intermediate global risk (10% to 20% risk of CHD per 10 years).

Patients with a marked or persistent elevation of hs-CRP (>10mg/L) after repeated testing should be evaluated for noncardiovascular inflammatory processes.

In patients with established coronary disease, CHD risk equivalents, or acute coronary syndromes, hs-CRP measurement may be a marker for prognosis; however, these patients should receive maximal aggressive treatment regardless of CRP level. Serial hs-CRP testing should not be used to monitor the effects of treatment.

No specific treatment for individuals with an elevated hs-CRP has been shown to reduce morbidity and mortality. Thus, while risk stratification using the hs-CRP may be accurate, it is uncertain that this classification adds benefit beyond traditional risk factor management.

All strength of recommendation level C

Reference

Pearson TA, et al. *Circulation*. 2003;107:499-511.

loss, smoking cessation) and evaluation and treatment of other conditions that indicate systemic inflammation, such as poor dental health, *Chlamydia pneumoniae*, cytomegalovirus, and other infections.

Additionally, the potential effects of hormone therapy (HT) on CRP levels should be evaluated in selecting the appropriate treatment for vasomotor symptoms. Route of administration may be of consequence: elevated levels of CRP have been associated with oral but not with transdermal HT. Interestingly, the American Society for Reproductive Medicine HT guidelines suggest that route of HT administration may have an effect on potential risk.²

■ PROGRESSION TO DIABETES, RISK FOR CVD, AND CRP

In identifying patients at risk for CVD, the relation among insulin resistance (also called the metabolic syndrome, syndrome X, or the Reaven syndrome), diabetes, and CVD should be considered. Approximately 75% to 80% of people who eventually develop type 2 diabetes, currently about 47 million in the United States, first exhibit the metabolic syndrome.³ Treatment of this condition has been shown to prevent or slow the progression to diabetes.

The metabolic syndrome consists of a cluster of metabolic and lipid abnormalities that puts patients at increased risk for both diabetes and CVD. According to the National Cholesterol Education Program's Adult Treatment Guidelines III (ATP III), diagnosis requires at least 3 of 5 criteria:

- Abdominal obesity, as measured by a waist circumference of more than 40 inches (102 cm) in men and 35 inches (88 cm) in women
- A triglyceride level of 150 mg/dL or more
- A high-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dL in men and 50 mg/dL in women
- Blood pressure equaling or exceeding 135/85 mg/dL
- Impaired fasting glucose of greater than 110 mg/dL.⁴

Additionally, recent investigations have demon-

strated that the metabolic syndrome is associated with a systemic inflammatory response to acute injury, infection, or other inflammatory stimuli.⁵ Similarly, systemic inflammation—and the presence of numerous cell types and inflammatory molecules—is a major feature of atherosclerosis.⁶ It is, therefore, not surprising that many patients with the metabolic syndrome also share a marker of inflammation, hs-CRP, associated with atherosclerosis and elevated CVD risk.⁷

C-reactive protein is now recognized as part of the inflammatory process through which atherosclerosis forms. It is an acute-phase protein produced by the liver in response to cytokine production (interleukins [IL] 1 and 6, tumor necrosis factor) during tissue injury, inflammation, or infection.⁸ Deposited in the arterial wall, CRP binds to low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein, a process linked to the onset of arteriosclerosis.⁹

The increasing recognition that inflammatory markers are part of the inflammatory process of atherosclerosis suggests a biologic plausibility for their potential use as indicators or predictors of atherogenesis or atherosclerosis.¹⁰ Menopausal hormonal changes also impact CRP.

■ CRP LEVELS, THE METABOLIC SYNDROME, AND CVD EVENTS

The extent to which elevated levels of CRP correlate with the metabolic syndrome and CVD events was shown in a prospective study of 14,719 initially healthy women who were followed over 8 years. The women were participating in the Women's Health Study, a continuing study of the efficacy of aspirin and vitamin E in preventing CVD.¹¹ A steady linear increase in CRP levels was seen as the number of metabolic syndrome components rose. As metabolic syndrome components increased from 1 to 5, median CRP levels were 1.09, 1.93, 3.01, 3.88, and 5.75 mg/L, respectively. The median CRP level was 0.68 mg/L in women who did not have the syndrome (Figure 1).

CRP levels and first CVD event

This study also matched CRP levels to a first CVD event, which included nonfatal myocardial infarct-

tion (MI), nonfatal ischemic stroke, coronary revascularization procedures, and CVD-related death. Women with the metabolic syndrome and a CRP value of more than 3 mg/L were at a higher relative risk for a future CVD event than women with or without the metabolic syndrome and a CRP level of less than 3 mg/L. The authors noted that CRP added important and independent prognostic information regarding future cardiovascular risk at all levels of severity of the metabolic syndrome.

Predictive value of CRP

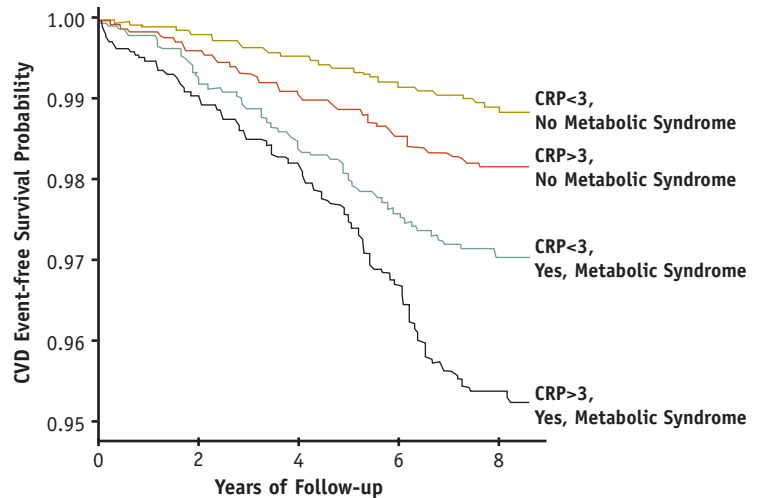
Of particular interest to clinicians, the marker can be detected in apparently healthy individuals before the onset of disease—and, thus, help predict the likelihood of future CVD events. Multiple lines of evidence show that CRP is independently predictive of cardiovascular events.

In 1 study, baseline blood samples from 122 apparently healthy women who had experienced their first CVD event were obtained and compared with 244 age- and smoking-matched control subjects who did not have a CVD event during a 3-year follow-up.¹² Women with higher baseline levels of CRP experienced a CVD event significantly ($P = .0001$) more often than the control subjects. Those with the highest levels of CRP (>7.3 mg/L) at baseline had a 5-fold greater risk for any vascular event than control subjects did and a 7-fold higher risk for stroke or MI ($P = .0001$ for both).

This test becomes particularly helpful to a physician when dealing with a patient at intermediate risk for a cardiovascular event by standard risk assessment. Elevated hs-CRP can be used to underscore the need for more aggressive risk reduction in a woman who may fall into the gray zone as to whether or not to lower her cholesterol. In addition, the Jupiter Trial (a large-scale, multicenter, placebo-controlled trial) is assessing

FIGURE 1

hs-CRP adds prognostic information to the ATP-III definition of the metabolic syndrome (n = 14,719)



Ridker PM, et al. *Circulation*. 2003;107:391-397.¹¹

whether or not lipid lowering in patients with LDL levels lower than 130 mg/dL but with elevated CRP levels will benefit from primary prevention with statins.

Assessing a patient's risks for CVD

Analysis of CRP is useful as an adjunct to—not as a substitute for—analysis of traditional major and other risk factors. Any single major risk factor (Table 1) has the potential to lead to CVD; these traditional risk factors should be evaluated to determine absolute risk; Framingham risk scoring provides an acceptable tool for most white, Hispanic, and black Americans. Individuals of South Asian origin appear to have about 2 times the absolute risk for any set of risk factors in comparison with whites. However, other risk factors also must be evaluated and their potential impact on the patient's overall risk assessed. In this light, measurement of CRP levels can provide important information.

The World Health Organization has established standards for hs-CRP. Tests for hs-CRP provide consistent and reproducible results. Tests are inexpensive and can be ordered with routine blood work; however, only testing for hs-

TABLE 1

Traditional Major Risk Factors for CVD

Major independent risk factors

- Cigarette smoking
- Hypertension
- Elevated serum total (and LDL) cholesterol
- Low serum HDL cholesterol
- Type 2 diabetes
- Advancing age

Other risk factors

- Predisposing risk factors
 - Obesity
 - Physical inactivity
 - Family history of premature coronary heart disease
 - Ethnic characteristics
 - Psychosocial characteristics
- Conditional risk factors
 - Elevated serum triglycerides
 - Small LDL particles
 - Elevated serum homocysteine
 - Elevated serum lipoprotein(a)
 - Prothrombotic factors (eg, fibrinogen)
 - Inflammatory markers (eg, C-reactive protein)

CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Data from Grundy SM, et al. AHA/ACC Scientific Statement. *Circulation*. 1999;100:1481-1492.

CRP (not standard CRP) provides clinically useful information. Assays have not been standardized for lipoprotein(a), total homocysteine, tissue plasminogen activator, plasminogen activator inhibitor-1, and fibrinogen,¹³ making them less useful for risk assessment.

The accuracy of prediction models for a CVD event that included or excluded CRP have been evaluated. Models using CRP in addition to traditional risk factors provided a significantly ($P = .005$) better method to predict risk than models that excluded CRP (Figure 2).¹⁴

CRP vs LDL: predictive value for CVD events

C-reactive protein may more effectively predict CVD risk than do LDL levels. In a comparison of CRP and LDL-C, a prospective study followed 27,939 apparently healthy postmenopausal women for 8 years.¹⁵ Women in the higher quintiles of CRP levels had a greater risk for a CVD event across the 10-year Framingham risk categories and across the LDL-C categories. C-reactive protein was more effective in predicting risk for a CVD event for the composite clinical endpoint and for each component: CRP and LDL-C levels correlated minimally and consequently identified different high-risk groups. Using both indicators would

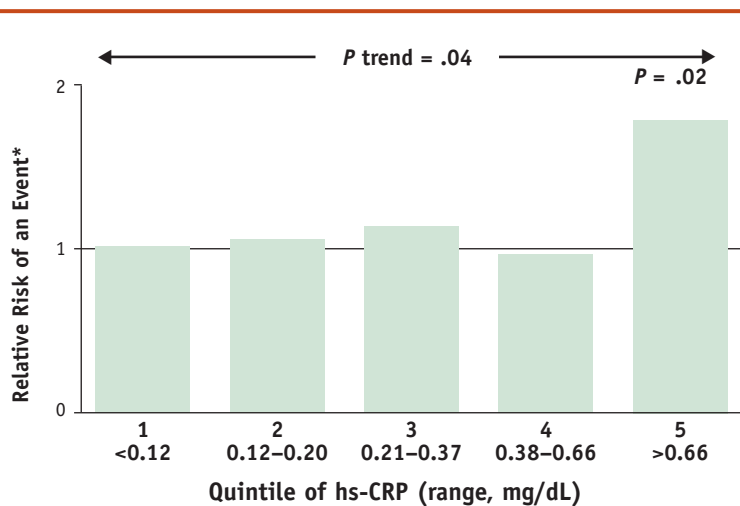
provide more accurate prognostic information than employing either one alone.

CRP, HT, and risk for cardiovascular events

The results of the Women’s Health Initiative (WHI) have raised concerns about the potential risk for adverse cardiovascular events in women receiving HT. However, as has been discussed in “The Menopausal Transition: How Does Route of Delivery Affect the Risk/Benefit Ratio of Hormone Therapy?” by Lee P. Shulman, MD (page S13), the WHI enrolled a population significantly older than the recently menopausal

FIGURE 2

CARE: hs-CRP and relative risk of recurrent coronary events



*Recurrent myocardial infarction or death from coronary heart disease. hs-CRP, high-sensitivity C-reactive protein. Ridker PM, et al. *Circulation*. 1998;98:839-844.¹⁴

patient who would typically use HT. The study was not designed to evaluate effectiveness of HT in controlling menopausal symptoms or the impact of HT on CVD risk for women experiencing menopausal symptoms. Further, only one HT formulation, dosage, and route of delivery was used in the study.

Clinical studies have shown that oral HT raises CRP levels because orally administered estrogen has a first-pass metabolism in the liver, where CRP is synthesized. The implications of these effects remain uncertain. However, the potential effects of CRP elevation should be considered, particularly in patients who do not respond to low-dose formulations, are concerned about the potential CVD risk demonstrated in the WHI, or prefer not to take pills.

The potential impact of HT on CRP levels may, for some patients, provide a rationale for hs-CRP testing. Additionally, hs-CRP can contribute to the overall assessment of global risk for CVD, in terms of both traditional major risk factors and other risk factors. A further substudy from the WHI underscores the relation between oral HT use, CRP and IL-6 levels, and vascular risk.¹⁶

In this prospective, nested case-control study of postmenopausal women, 304 women with no previous history of CHD or cancer and who developed incident CHD were matched by age, smoking status, ethnicity, and follow-up time with 304 event-free study participants. At 2.9 years of follow-up, incidence of first MI or death from CHD was assessed. Median baseline levels of CRP (0.33 vs 0.25 mg/dL; interquartile range [IQR], 0.14–0.71 vs 0.10–0.47; $P < .001$) and IL-6 (1.81 vs 1.47 pg/mL; IQR, 1.30–2.75 vs 1.05–2.15; $P < .001$) were significantly higher among cases compared with controls.

In matched analyses, the odds ratio (OR) for incident CHD in the highest vs lowest quartile was 2.3 for CRP (95% confidence interval [CI], 1.4–3.7; P for trend = .002) and 3.3 for IL-6 (95% CI, 2.0–5.5; P for trend $< .001$). After further adjustment for lipid and nonlipid risk factors, both CRP and IL-6 were significantly associated with a 2-fold increase in odds for CHD events. Current HT use was associated with significantly elevated median

CRP levels; no association between HT and IL-6 was observed. A positively graded relation between plasma CRP levels and the OR for CHD was seen among both users and nonusers of HT across the full spectrum of baseline CRP. This indicated that elevated CRP and IL-6 levels independently predict vascular events among apparently healthy postmenopausal women and the elevation in CRP seen with oral HT leads to increased risk.

Markers of inflammation

A recent study investigated changes in the levels of markers of inflammation (including CRP), fibrinolysis, and procoagulation in 230 women receiving unopposed estrogen, 60 receiving estrogen/progestin, and 196 controls. Compared with the control group, women (mean age of 72.9 years) using estrogen had a 59% increase in mean CRP ($P < .001$) but a moderate decrease in the other markers. With the women (mean age of 72.6 years) receiving combined HT, CRP levels were elevated in women in the second and third highest tertiles stratified by body mass index.¹⁷ This increase may have resulted from the inflammatory effect of the formation of adipocyte tissue.

Oral vs transdermal HT and CRP levels

Three studies have indicated that estrogen's effect on CRP appears to be related to oral administration. A 3-period crossover study with 21 postmenopausal women compared the effects of route of HT administration on levels of CRP, 3 other inflammatory markers, and the anti-inflammatory insulinlike growth factor-1 (IGF-1). The study focused on whether the first-pass hepatic metabolism of oral HT causes the estrogen-related elevation of CRP. The women received 8 days of transdermal estradiol (E2) plus an oral placebo, oral conjugated equine estrogen (CEE) plus a placebo transdermal patch, and an oral and transdermal placebo.

Oral CEE increased hs-CRP levels nearly 4-fold from baseline, but transdermal E2 did not affect CRP (**Figure 3**). Oral CEE, but not transdermal E2, reduced levels of IGF-1, with the decline in IGF-1 levels inversely correlating with the magnitude of

increase of CRP ($P = .008$).¹⁸ In a randomized, double-blind study of 152 postmenopausal women who had hysterectomies, oral estrogen significantly ($P = .004$) increased CRP levels compared with placebo. No significant changes occurred in the transdermal group compared with placebo.¹⁹ In a randomized, 6-month study of 189 postmenopausal women between 48 and 55 years of age, oral CEE increased CRP levels by 48%, while the increase with transdermal estrogen was 10%.²⁰

Similarly, the association of venous thromboembolism (VTE) with oral and transdermal formulations recently was studied in a multicenter, hospital-based, case-control study of postmenopausal women.²¹ One hundred and fifty-five consecutive patients with a first documented episode of idiopathic VTE (92 with pulmonary embolisms and 63 with deep venous thromboses) were compared with 381 controls. Overall, 32 (21%) patients who had had VTE and 27 (7%) controls were current users of oral HT, whereas 30 (19%) patients and 93 (24%) controls were current users of transdermal HT.

After adjustment, the estimated risk for VTE in current users of oral HT compared with transdermal HT users was 4.0 (95% CI, 1.9–8.3). The investigators suggest that oral but not transdermal HT is associated with risk of VTE in postmenopausal women. These data suggest that transdermal HT might be safer than oral HT in terms of thrombotic risk.

Statins, HT, and CRP levels

HMG-CoA reductase inhibitors (statins) have been shown to modify CRP in various trials and have demonstrated effectiveness in reducing CRP levels in women taking oral HT. In a recent post hoc evaluation of the HERS data, patients

who were receiving treatment with statins were compared with women who were not receiving treatment with these agents.

The investigators reported that statin therapy was associated with a reduced incidence of VTE in both the HT and placebo study arms. The negative effect of HT on the primary outcome—MI and death resulting from CHD—was reduced (MI or fatal CHD, relative hazard [RH] = .78; 95% CI, 0.61–0.99; $P = .044$), as was all-cause mortality (RH = .74; 95% CI, 0.56–0.99; $P = .04$). Incidence of VTE was reduced in both the HT and placebo participants receiving statins. The authors concluded that the use of statins may attenuate the increased risk of CVD in women who use oral HT.²²

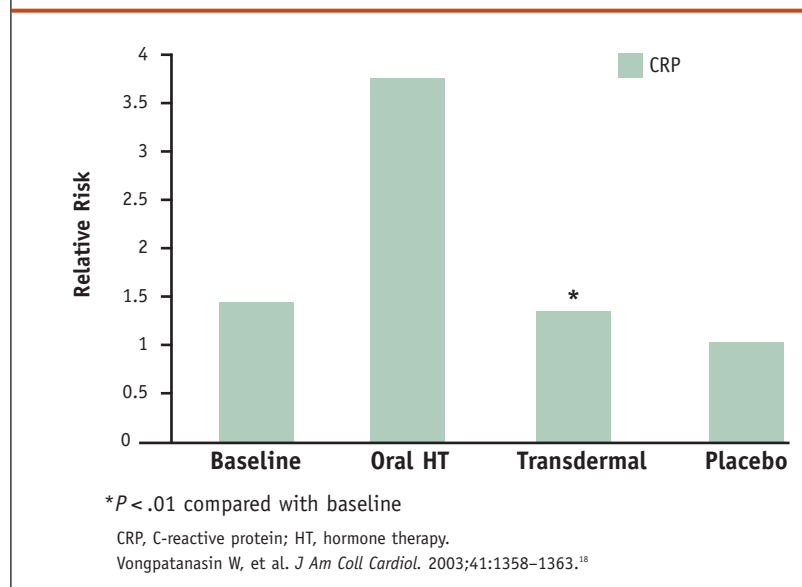
PRACTICE GUIDELINES

The results of the clinical and prospective studies of CRP indicate that serious consideration should be given to adding the inflammatory marker to screening guidelines for risk for a first-time CVD event. Reasons for doing so are:

- C-reactive protein has been shown to be a more accurate predictor of future CVD events than is LDL-C, and CRP adds to the prognostic information of the Framingham Risk Score.

FIGURE 3

Effects of oral vs transdermal estrogen



- C-reactive protein predicts type 2 diabetes and adds prognostic information on vascular risk at all levels of the metabolic syndrome.
- Regarding population risk, the proportion of CVD that might be prevented by reducing inflammation may exceed that achieved by reducing LDL-C levels. However, no evidence is currently available that decreasing CRP levels will necessarily reduce risk.
- Measurements of CRP and LDL-C levels tend to detect different high-risk groups, so combined screening with both biomarkers is superior to the use of either alone. In primary prevention, people with high CRP/low LDL-C are at higher absolute risk than are people with low CRP/high LDL-C.
- New American Heart Association guidelines note that all high-risk women should receive lipid-lowering therapy, preferably with statins. Patient evaluation should be made using the Framingham score and other risk factors.
- Women using HT should be evaluated individually concerning the potential impact of route of administration.
- Hormone therapy is not recommended for cardiovascular protection.
- The potential cardiovascular impact of HT and route of administration should be evaluated in terms of potential for elevated CRP levels.

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Posttest

Please select the best answer to each of the following 10 questions and record the answers on the CME Registration/Posttest Answer Form/Evaluation (page S25).

Expiration date for credit: June 30, 2006

- Newer third-generation oral contraceptives (OCs) containing progestins derived from 19-nortestosterone, such as desogestrel and norgestimate, have lower levels of androgenicity than do formulations containing earlier progestins, such as levonorgestrel.
 - True
 - False
- Ovarian activity is more effectively suppressed with a hormone-free interval of 7 days vs a hormone-free interval of 4 days.
 - True
 - False
- What percentage of reproductive-age women report symptoms associated with their menstrual periods?
 - 40% to 60%
 - 70% to 90%
 - 50% to 70%
 - 60% to 80%
- Use of an OC with antimineralocorticoid activity reduces the bloating effect commonly experienced with OC use.
 - True
 - False
- OCs containing which progestin may be effective in treating premenstrual symptoms and premenstrual dysphoric disorder?
 - Drospirenone
 - Norgestimate
 - Levonorgestrel
 - Gestodone
- Administration of oral hormone therapy (HT) has been associated with an increase in triglyceride (TG) levels, while transdermal HT has been shown to lower TG levels.
 - True
 - False
- In a recent study, the risk for venous thromboembolism was increased with the use of oral estrogen but not with transdermal estrogen.
 - True
 - False
- Levels of C-reactive protein (CRP) have been shown to increase when which HT regimens are used?
 - Oral
 - Transdermal
 - Low-dose oral or transdermal
 - Route of administration does not affect CRP levels
- Which findings of the Women's Health Initiative were similar to those of earlier observational trials?
 - Increased risk of venous thromboembolic events
 - Decreased risk for hip fracture
 - Decreased risk for colon cancer
 - Increased risk for stroke
 - All of the above
- Prediction models that have been shown to more accurately predict cardiovascular disease events include
 - Only traditional risk factors for heart disease
 - Traditional risk factors and CRP
 - Traditional risk factors, CRP, and fibrinogen
 - Only CRP

THE JOURNAL OF FAMILY PRACTICE

A CME Supplement to
THE JOURNAL OF FAMILY PRACTICE July 2004

Key issues in women's healthcare

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