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INSIDE

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HRT studies cut through confusion on breast cancer, coronary heart disease

Risks slightly increase — Should you change your current practice?

Two new studies indicate a modestly increased risk of developing breast cancer among women using estrogen/progestin combination hormone replacement therapy (HRT) compared with those using estrogen-only therapy (ERT).[1,2] A preliminary update from the Women's Health Initiative states that during the first two years of the national study, a small increase in the number of heart attacks, strokes, and blood clots has been noted in women taking active hormones compared with placebo pills.

How should you respond? Stay the course, advise two national professional societies, both of which have issued statements on the HRT/breast cancer issue. The statement by the American College of Obstetricians and Gynecologists in Washington, DC, reads, "Although these new studies add to the existing knowledge regarding this issue, particularly regarding combined estrogen-progestin regimens, ACOG does not recommend a change in clinical practice based on these new studies. Additional research is needed to better define the balance of risks and benefits of HRT use."[3]

EXECUTIVE SUMMARY

Two studies indicate a moderately increased risk of developing breast cancer among women who use combined estrogen/progestin therapy. A preliminary report from the national Women's Health Initiative notes a slight increase in the number of heart attacks, strokes, and blood clots in women taking active hormones compared with placebo pills.

- The American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine have issued statements on the hormone replacement therapy (HRT)/breast cancer studies and call for clinicians to continue in their current practice concerning HRT.
- An independent monitoring board has recommended continuation of the Women's Health Initiative study, which includes more than 27,000 women ages 50 to 79.

The society continues to recommend that practitioners consider HRT to relieve vasomotor symptoms, genitourinary tract atrophy, and mood and cognitive disturbances associated with menopause, as well as to reduce osteoporosis and cardiovascular disease. ACOG plans publication later this year of a new committee opinion on the issue of breast cancer and HRT.

The American Society for Reproductive Medicine (ASRM) "maintains its current recommendation for use of HRT in healthy post-menopausal women," reads the statement on HRT and breast cancer from the Birmingham, AL-based group.[4] "Furthermore, it is imperative that physicians continue to discuss risks and benefits of HRT individually with each woman considering therapy, including the need for regular mammographic screening and preventive health care."

For those who are seeing women enrolled in the Women's Health Initiative, encourage their continued participation in the clinical trial, advises **Leon Speroff**, MD, professor of obstetrics and gynecology at Oregon Health Sciences University in Portland.

"Because the events in the Women's Health Initiative occurred early, followed by a reduction, clinicians should encourage participants in the study to remain enrolled, impressing upon them the importance of this large clinical trial," Speroff says. **(See story, p. 68, for information on the Women's Health Initiative's preliminary report.)**

Examine the JAMA *data*

In the first study dealing with HRT use and breast cancer, published in *The Journal of the American Medical Association* (*JAMA*), researchers from the National Cancer Institute (NCI) in Rockville, MD, analyzed follow-up information from 46,355 post-menopausal women who participated in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. The scientists compared the new cases of breast cancer with the type of hormone replacement therapy used for this group of women who had no previous evidence nor diagnosis of breast cancer.

Most of the data in the study referred to the sequential regimen where progestins were given for fewer than 15 days per month, says lead author **Catherine Schairer**, PhD, of the NCI's Division of Cancer Epidemiology and Genetics. The regimen being tested in the Women's Health Initiative is the combined continuous regimen where both estrogen and progestin are given daily, she notes. The researchers identified 2,082 cases of breast cancer during the 1980 through 1995 follow-up period.

The *JAMA* study found that increases in breast cancer risk associated with HRT were primarily among recent users of HRT (current and past use occurring within the previous four years). The relative risks were 1.2 for estrogen-only users and 1.4 for those on a combination regimen. The relative risk refers to the risk of outcome in the exposed population (HRT users) relative to that in the unexposed or control population (non-HRT users). A relative risk greater than 1.0 implies an increased risk.

"Our results suggest that the combined estrogen-progestin regimen is associated with greater increases in breast cancer risk than estrogen alone," the authors write. "Assessing the comparative risk of estrogen alone vs. estrogen-progestin was complicated by the fact that use of estrogen alone was associated with increased risk in lean but not heavy women." The authors found differences between the two regimens (estrogen-only and estrogen-progestin HRTs) among lean women, but they were unable to draw conclusions among heavier women.

According to the ASRM statement, the women included in the study were much more apt to have had a surgical consultation or breast biopsy, characteristics that are risk factors for breast cancer, than were all women in the same age group.[4] Also, the study relied on the women for historical recall as to whether they took a progestin, and the dose and type of progestin might be different from those now administered. Moreover, the risk of breast cancer was increased only among thin

COMING IN FUTURE MONTHS

- Tips to encourage condom use
- New pills with shortened pill-free intervals
- Monthly injectable contraceptive: Patient information
- Update on contraceptive vaginal ring
- Vaginal contraceptive pills

women with a body mass index of 24.4 kg / m^2 or less.

"Is there a slight risk of breast cancer [in lean women] with long exposure to estrogen-progestin, or is this a problem of an imprecise conclusion in a range easily affected by biases and small numbers?" asks Speroff. "I don't know the right answer, but, in my view, the relative risks are not high enough or precise enough to allow a definitive clinical conclusion."

Review JNCI *data*

In the second study, published in the *Journal of the National Cancer Institute (JNCI*), researchers looked at women with incident breast cancers diagnosed over four years in Los Angeles County, CA, in the late 1980s and 1990s. Control subjects were neighborhood residents individually matched to case subjects in age and race. Case subjects and control subjects were interviewed in person to collect information on known breast cancer risk factors as well as HRT use. Information on 1,897 post-menopausal case subjects and on 1,637 post-menopausal control subjects ages 55 to 72 years who had not undergone a simple hysterectomy was analyzed for the report.

The *JNCI* study findings indicate a greater increased risk of breast cancer associated with the use of estrogen and progestin compared with estrogen alone. Researchers further note that a sequential combination of estrogen and progestin was associated with a greater risk of breast cancer than the risk associated with a daily continuous regimen of estrogen and progestin.

The *JNCI* study found that any HRT regimen was associated with a 10% higher breast cancer risk for each five years of use (odds ratio of 1.10). Risk was higher for estrogen-progestin use, with an odds ratio of 1.24, than for HRT using estrogen alone (odds ratio of 1.06). The odds ratio indicates the ratio of the odds of being exposed to an agent in the case group (i.e., those who developed breast cancer who used HRT) relative to the odds in the control group.

Ronald Ross, MD, professor and chairman of the department of preventive medicine at the University of Southern California's Norris Comprehensive Cancer Center in Los Angeles, says the take-home message from the two recent studies should be the need for developing a delivery system that targets progestins directly to the endometrium to diminish risks of endometrial cancer.

"Certainly the cardiovascular system doesn't want much to do with progestins, [and] this certainly shows you that the breast doesn't want much to do with progestins post-menopausally," he observes. "Let's figure out a way to get it to the organ that really needs it and wants it menopausally."

Is there cause for concern about use of hormone therapy when it comes to breast cancer? Not at the present time, states **Trudy Bush**, PhD, MHS, professor in the department of epidemiology and preventive medicine at the University of Maryland at Baltimore and adjunct professor of epidemiology at Johns Hopkins University, also in Baltimore. Her observations have not changed since she published the following in a *JAMA* editorial:

"Does ERT increase the risk of breast cancer? After more than five decades of ERT use in the United States and scores of epidemiological studies, this question still cannot be answered definitively," she wrote. "In contrast, the association between ERT and endometrial cancer was clearly established nearly 25 years ago by epidemiological studies. At this time the absence of convincing evidence of an association between ERT and breast cancer risk should be reassuring."[5]

How can providers address the issue with patients? Stress the benefits of post-menopausal hormone therapy; point out the continuing concern regarding the relationship between estrogen use and breast cancer (particularly long-term use); and emphasize the absence of definitive evidence linking such therapy to an increased risk of breast cancer, as well as the uniform data indicating better outcomes in hormone users who develop breast cancer, Speroff says.

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Update won't stop Women's Health Initiative

Women who are participating in the hormone replacement therapy (HRT) component of the Women's Health Initiative (WHI) have been notified of a small increase in the number of heart attacks, strokes, and blood clots during the first two years of the national study in those taking active hormones.

"Over time, these differences seem to get smaller and may even disappear," states a patient update issued by the WHI.[1] "In fact, overall, WHI women had fewer such events than would be expected in the general population."

While the WHI has alerted women of these findings, it also is emphasizing that its independent monitoring board recommends continuation of the study. Such reassurance is important given the reports of increased risks published in lay press, says **Susan Wysocki**, RNC, NP, president and chief executive officer of the Washington, DC-based National Association of Nurse Practitioners in Women's Health.

"Apparently, the actual risk found in the treatment group, [which was] less than 1%, is still lower than the general population, but HRT makes big news," observes Wysocki. "I just hope this does not throw off the WHI, because we need that data."

HRT effects examined

The National Institutes of Health in Bethesda, MD, established the 15-year Women's Health Initiative, one of the largest U.S. prevention studies of its kind, to address the most common causes of death, disability, and impaired quality of life in post-menopausal women. The HRT component of the study is examining the effects of HRT on heart disease, osteoporosis-related bone fractures, and breast and endometrial cancer.

More than 27,000 women ages 50 to 79 are participating in the HRT study. Women with uteruses have been randomized to receive estrogen plus progestin or a placebo, and women who have had hysterectomies have been randomly selected to receive estrogen alone or a placebo.

Women in the WHI trial are evaluated at least every six months by local clinic staff to make sure it is safe for them to stay on study pills. Local results are examined by a human subjects committee. An independent group of medical experts, the Data and Safety Monitoring Board (DSMB), reviews information from all participating clinics nationwide.

"Both your local clinic's human subjects committee and the DSMB have the power to stop or change the study if they find important safety concerns," the WHI patient update reads. "They have not done so. In fact, the DSMB has recommended that the study continue."

Challenging the belief

The information issued by the WHI comes on the heels of two clinical trials that have challenged the belief that post-menopausal hormone therapy protects against coronary heart disease.[2,3]

The first study, the Heart and Estrogen / progestin Replacement Study (HERS), was a randomized, double-blind, placebo-controlled study of estrogen plus progestin therapy in post-menopausal women with established coronary heart disease. The clinical trial included 2,763 participants ages 44 to 79 who had atherosclerosis, experienced a heart attack, or undergone bypass surgery or angioplasty. Patients were randomized to receive Prempro [an HRT product containing conjugated estrogens and medroxyprogesterone acetate (MPA), manufactured by Wyeth-Ayerst Laboratories of Philadelphia] or placebo.

A follow-up study is planned to see whether the beneficial trend seen in the past two years continues.

Researchers found that the estrogen / progestin combination did not decrease the overall risk of heart attack and coronary death among post-menopausal women with previous heart disease. The studied regimen appeared to increase the risk of heart attack in the first year of treatment and then to decrease it after two years of treatment. An observational follow-up study (HERS II) is planned to determine whether the beneficial trend seen in the last two years of the trial continues.

The second study, the Estrogen Replacement and Atherosclerosis (ERA) trial, was designed to determine the effect of unopposed estrogen or combined estrogen-progestin therapy on the progression of coronary artery disease in

post-menopausal women with existing coronary disease. A total of 309 older women were randomly assigned to take estrogen, estrogen combined with a progestin, or a placebo. Researchers found that progression of atherosclerosis was not affected by 3.2 years of treatment with either unopposed estrogen or a combination of estrogen and MPA.

Statins, a class of drugs that lower cholesterol levels, have been shown to reduce the risk of coronary events by approximately 30% (greater in higher-risk individuals) in men and women.[4,5] These drugs include atorvastatin (Lipitor from Parke-Davis in Morris Plains, NJ), lovastatin (Mevacor from Merck & Co. of West Point, PA), simvastatin (Zocor from Merck & Co.), pravastatin (Pravachol from Bristol-Myers Squibb Co. of Princeton, NJ), and fluvastatin (Lescol from Novartis Pharmaceuticals Corp. of East Hanover, NJ).

Be conservative in some cases

Leon Speroff, MD, professor of obstetrics and gynecology at Oregon Health Sciences University in Portland, says, "These trial results are reasons to be conservative regarding hormone therapy for older women with evidence of coronary heart disease; certainly, we should not promote estrogen as a first-line drug to prevent further clinical events in women with coronary artery disease, especially in women who have had a recent myocardial infarction."

Multiple clinical trials have established that treatment with statins is very effective in preventing clinical cardiac events, Speroff adds.

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Push is on for increased microbicide R&D funds

Products are in phase III trials

At least 12 million American women are waiting for them. More than 600 scientists from around the globe just met to discuss the latest research about them. Yet despite this interest, there still are no microbicides on the U.S. market with proven effectiveness against infection by HIV and sexually transmitted disease (STD) pathogens.

However, recently introduced legislation in Congress may help increase the federal investment in microbicide research. Rep. Connie Morella (R-MD) has introduced H.R. 3891, the Microbicides Development Act of 2000, which calls for enlarging the $25 million now earmarked for microbicide development to $50 million in fiscal year 2001 and $75 million in fiscal year 2002.

To protect themselves from the risk of HIV/AIDS and other STDs, women now can use a female condom or negotiate male condom use with their partners. While nonoxynol-9 (N-9), now used as a spermicide in pregnancy prevention, does offer some protection against bacterial STDs such as gonorrhea, chlamydia, and trichomoniasis, its ability to prevent the transmission of viral STDs, particularly HIV, is under question. **(*Contraceptive Technology Update* offered an update on N-9 research in its April 1999 issue, p. 40.)**

Vaginal microbicides offer a self-controlled

EXECUTIVE SUMMARY

New legislation has been introduced in Congress for increased funding for research and development of microbicides, which protect against HIV and sexually transmitted diseases.

- Proceedings from the first international conference on microbicides are to be published this summer.
- Two products marketed in the United States as spermicides are now in phase III trials to examine their effectiveness as microbicides.
- A national survey of U.S. women ages 18 to 44 shows that 94% would be interested in using a microbicide if they ever found themselves at risk for STD infection.

method of protection that does not require partner knowledge or cooperation. Mechanisms of action include:

- blocking infection by creating a barrier between the pathogen and the vagina;
- killing or immobilizing pathogens;
- preventing a virus from replicating once it has infected the cells that line the vaginal wall.[1]

Coordinating efforts

In addition to increased funding, the proposed legislation also calls for creating a program under the auspices of the National Institutes of Health (NIH) in Bethesda, MD, to coordinate microbicide research efforts now taking place in governmental agencies such as the NIH and the Atlanta-based Centers for Disease Control and Prevention (CDC), says **Heather Boonstra**, MA, senior public policy associate with the Alan Guttmacher Institute. The legislation also asks those agencies to develop a five-year implementation plan regarding microbicide research and development, she notes.

"What we are looking at is the fact that there are about 60 products now that are in the developmental pipeline that aren't moving as quickly as we would like," explains Boonstra. "This is trying to streamline some of that process."

In 1996, Secretary of Health and Human Services Donna Shalala announced that the federal government would invest $100 million ($25 million per year) in microbicide development over four years.[1] An accounting of funds spent the following year showed that 73% was earmarked for microbicide product development and testing, while the rest was allocated for basic research with multiple purposes that may have some application to microbicides.

For example, if a question on the National Survey of Family Growth addressed spermicide use, it was attributed to microbicide research, says Boonstra. By calling for funds to be earmarked for product research and development, advocates hope dollars will translate into progress in delivering a safe, effective product.

When such a product does arrive, it will be greeted with much interest. A nationally representative survey of U.S. women ages 18 to 44 shows that 94% would be interested in using a microbicide if they ever found themselves at risk for STD infection.[1]

The first international conference on microbicides just ended its inaugural three-day session with outstanding results, says **Polly Harrison**, PhD, director of the Alliance for Microbicide Development in Takoma Park, MD. Conference sponsors included the Alliance; American Foundation for AIDS Research in New York City; the CDC; Center for Health and Gender Equity in Takoma Park, MD; Contraceptive Research and Development Program in Arlington, VA; Family Health International in Research Triangle Park, NC; International AIDS Society in Stockholm, Sweden; Joint United Nations Programme on HIV / AIDS (UNAIDS) in Geneva, Switzerland; the NIH; Office of AIDS Research in Bethesda, MD; Population Council in New York City; and the United States Agency for International Development in Washington, DC.

More than 600 attended, with about 43% coming from outside the United States, Harrison says. Information was shared regarding products in development, basic science issues, clinical questions, and behavioral and public health issues. Proceedings of the conference are to be published this summer in the journal *AIDS* (International AIDS Society, Stockholm, Sweden), says **Judith Auerbach**, PhD, behavioral and social science coordinator in the Office of AIDS Research.

Products in phase III

Just two microbicide products, Conceptrol Gel (manufactured by Ortho-McNeil Pharmaceuticals of Raritan, NJ) and Advantage-S (manufactured by Columbia Laboratories of Aventura, FL) are in phase III trials, reports **Ronald Roddy**, MPH, senior epidemiologist at Family Health International. Both of these products are commercially available in the U.S. market as spermicides.

Roddy's study on microbicidal use of Conceptrol and the UNAIDS investigation of similar use for Advantage-S will not be finished until later this year, says Roddy. A separate study of Conceptrol sponsored by the NIH and HIV Network for Prevention Trials (HIVNET) is just starting and will run for about three years, Roddy notes. HIVNET is a multicenter, collaborative research network founded by the Division of AIDS in the National Institute of Allergy and Infectious Diseases in Bethesda, MD.

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Osteoporosis: Stop the 'bone robber'

Your next patient is a 52-year-old Caucasian whose daily diet consists primarily of fast-food items and diet caffeinated sodas. She smokes 10 to 12 cigarettes per day, drinks two to three alcoholic beverages per day, and leads a sedentary lifestyle. Is she at risk for osteoporosis?

Yes, and she is not alone, according to statistics from the National Institutes of Health (NIH) in Bethesda, MD.[1] About 10 million people in the United States have osteoporosis, which makes it the most prevalent metabolic bone disorder in this country. An additional 18 million individuals already have low bone mass, which places them at increased risk for this disorder.

National and international experts recently gathered at the NIH-coordinated Consensus Conference on Osteoporosis to discuss the latest research findings on osteoporosis. The second such event in 16 years, the conference focused on prevention, diagnosis, and therapy for the skeletal disorder, which is characterized by compromised bone strength predisposing to an increased risk of fracture.

"The conference showed that we have made a lot of progress," notes **Conrad Johnston**, MD, professor of medicine at Indiana University School of Medicine in Indianapolis and president of the National Osteoporosis Foundation in Washington, DC, a nonprofit, voluntary health organization dedicated to reducing the widespread prevalence of osteoporosis. "As usual, as you learn new things, there are new questions that arise," Johnston says.

Calcium is the specific nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis, according to a statement issued by the consensus panel.[2]

Keep calcium intake in mind when working with adolescent patients: Only 10% of girls and 25% of boys between ages 9 and 17 obtain an adequate amount of calcium — 1,300 mg per day — in their diet through the consumption of dairy products and vegetables.[2] Most adults should get 1,000 mg per day of total elemental calcium intake, or 1,500 mg for post-menopausal women not taking supplemental estrogen.[3]

Help patients boost calcium intake by including low-fat dairy products such as milk, yogurt, and cheese; dark green leafy vegetables such as broccoli, spinach, and collards; tofu; and almonds.[4] Remember to also discuss vitamin D intake, which is required for optimal calcium absorption. A daily intake of 400 to 600 IU has been established for adults.[2]

There is strong evidence that physical activity early in life contributes to higher peak bone mass, according to the findings issued by the NIH consensus panel.[2] Since exercise not only improves bone health, but increases muscle strength, coordination, and balance, it is an important part of an osteoporosis prevention program at any age.[4]

Evaluate estrogen's role

Although hormone replacement therapy remains a common treatment and prevention option in osteoporosis, more information is needed on how estrogen alone or in combination with other treatments reduces the incidence of fractures.

"I think one of the important points that came out of the conference is that, although we do have some information on estrogen, and we certainly have information on the efficacy of the bisphosphonates, particularly in terms of bone density, what we don't really have are long-term studies which can assess these particular therapies individually or in combination head to head," notes **Anne Klibanski**, MD, professor of medicine at Harvard Medical School in Boston and chair of the NIH consensus panel.

Reduction in estrogen production with menopause is the major cause of loss of bone mineral density during later life.[2] Estrogen is

EXECUTIVE SUMMARY

About 10 million people in the United States have osteoporosis, and an additional 18 million individuals already have low bone mass, which places them at increased risk for this disorder.

- Although hormone replacement therapy remains a common treatment and prevention option, an independent consensus panel recently convened by the National Institutes of Health suggested that more information is needed on how estrogen alone or in combination with other treatments reduces the incidence of fractures.
- New technologies have improved the detection of loss of bone mineral, a key predictor of osteoporotic fracture. However, the panel recognized that no standard exists for comparing different devices.

RESOURCE

- **National Osteoporosis Foundation**, 1232 22nd St. N.W., Washington, DC 20037-1292. Telephone: (202) 223-2226. Web: www.nof.org.

used to prevent osteoporosis in women who are at high risk for developing the disease, and it also is used to treat the disease after it has been diagnosed.[3]

Prevention and treatment alternatives to estrogen include the selective estrogen receptor modulator raloxifene (Evista, manufactured by Eli Lilly and Co. of Indianapolis) and the bisphosphonate alendronate sodium (Fosamax, manufactured by Merck & Co. of West Point, PA). Calcitonin (Miacalcin, manufactured by Novartis Pharmaceuticals, East Hanover, NJ) carries an indication for treatment of the disease. Another bisphosphonate, risedronate, has been shown to be effective in reducing nonhip-fracture risks in post-menopausal women.[5] The drug, marketed in the United States as Actonel by Procter & Gamble Pharmaceuticals of Cincinnati, currently is indicated for treatment of Paget's disease and does not carry a U.S. indication for prevention / treatment of osteoporosis.

The most commonly used measurement to diagnose osteoporosis and predict fracture risk is based on bone mineral density (BMD).[2] The World Health Organization in Geneva, Switzerland, has selected BMD measurements to establish criteria for diagnosing osteoporosis, expressed through a T-score, which is the number of standard deviations (SD) above or below the average BMD value. Osteoporosis is present when the T-score is at least minus 2.5 SD.

New technologies have improved the detection of loss of bone mineral. Dual energy X-ray absorptiometry (DXA) is the standard for measuring bone mineral density of the hip. Other measures of bone strength, such as ultrasound of the heel, are as effective in predicting hip fracture. However, the NIH panel recognized that no standard exists for comparing different devices and recommended collecting data necessary to establish testing guidelines for osteoporosis.

"I think that one of the things that the bone community and all physicians are grappling with is how do you standardize different measurements?" asks Klibanski. "One way, among many suggested, is to put a clinical trial into place to assess different therapies and different comparisons of therapies."

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Examine use of low- and lower-dose OCs

Are 20 mcg oral contraceptives (OCs) becoming more widely used? IMS Health, a Westport, CT-based pharmaceutical market research firm, pegs new U.S. prescriptions of such pills at 14%, and *Contraceptive Technology Update* readers see an uptick in their use.

"I am using more 20 mcg pills in my practice for women who have estrogen side effects, women over age 40 who are nonsmokers, women who are being watched for borderline hypertension or elevated cholesterol, and short-term use [12 weeks] for women who do not need it as a birth control method but want to regulate their menses for beginning menopausal changes or vacation schedules," says **Theresa Rundell**, ARNP, at Klickitat County Health Department in White Salmon, WA.

EXECUTIVE SUMMARY

The use of 20 mcg oral contraceptives (OCs) is gaining ground, as more providers are using them in a wider range of women.

- A recent study that compared two 20 mcg pills against a 35 mcg formulation indicates that while cycle control was similar among all three products, estrogenic side effects were 50% more common in women using the 35 mcg pill.
- Proper pill taking is an important component in ensuring the effectiveness of any OC. Clinicians should provide thorough education on pill usage with 20 mcg pills because they might be less forgiving of a missed pill in the daily regimen.

Some public health facilities have not yet incorporated use of 20 mcg pills into formularies due to cost, as is the case at San Antonio Metropolitan Health District. "The 20 mcg pills are currently too expensive for us to stock," says **Janet Realini**, MD, MPH, director of family planning. "It is my understanding that they are increasing in popularity and market share in the private practice world, especially among 'older' women taking oral contraceptives."

There are currently four 20 mcg pills:

- Alesse, an ethinyl estradiol (EE)/levonorgestrel(LNG) pill from Wyeth-Ayerst Laboratories of Philadelphia;
- Levlite, an EE/LNG formulation from Berlex Laboratories of Wayne, NJ;
- Loestrin, an EE/norethindrone acetate pill from Parke-Davis of Morris Plains, NJ;
- Mircette, an EE/desogestrel OC manufactured by Organon of West Orange, NJ.

When it comes to prescribing for "new start" patients, though, *CTU* readers continue to rely on a 35 mcg pill, Ortho Tri-Cyclen from Ortho-McNeil Pharmaceuticals of Raritan, NJ. Almost half of *CTU* readers participating in the newsletter's 1999 contraception survey picked the pill as first-line contraception for 21-year-old women. **(For more results of that survey, see *CTU*, September 1999, p. 97.)**

Direct comparisons of different OC formulations have been limited; however, a new study examines the side effects, cycle control, and continuation rates of women using Alesse, Mircette, or Ortho Tri-Cyclen.[1] A grant from Organon supported the randomized open-label multicenter clinical trial. The results? Such side effects as bloating, breast tenderness, and nausea were approximately 50% more common in women using the 35 mcg pill as compared with the 20 mcg preparations.

"The bottom line for our study was that it looks like the [20 mcg] pills have just as good cycle control, and they have statistically significantly less estrogenic side effects," says **Michael Rosenberg**, MD, MPH, clinical professor of obstetrics and gynecology at the school of medicine and adjunct professor of epidemiology at the school of public health, both at the University of North Carolina at Chapel Hill, and president of Health Decisions, a private research firm in Chapel Hill specializing in reproductive health. Rosenberg served as lead investigator for the trial.

A total of 463 women were randomized to use one of the three products, which were to be used for six menstrual cycles. Both "starters" and "switchers" (those who had used OCs in the previous three months before the study) were included in the investigation. Women were required to be between ages 18 and 50, have a body mass index of 18 to 35, and have regular menstrual cycles of 21 to 38 days.

"In this three-way comparison, we found fewer estrogenic side effects and equivalent cycle control and contraceptive efficacy in users of two 20 mcg EE preparations as compared to women using a 35 mcg EE OC," report the investigators. "The side effect findings were most striking, with consistent and significant elevations of approximately 50% in prevalence of estrogenic side effects in the higher-estrogen preparations."

Ortho Tri-Cyclen is the only OC with an indication for acne treatment approved by the Food and Drug Administration. In this particular study, however, when results from both starters and switchers were combined, no product-specific differences in decrease of acne achieved statistical significance. Self-reported acne decreased in starters by 19% and 43% in Alesse and Mircette users, while increasing 22% in Tri-Cyclen users. In switchers, there was less change, although Mircette users demonstrated a 16% decrease. Alesse users noted no change, and Tri-Cyclen users experienced a 22% increase.

Proper pill-taking is key

While 20-mcg OC formulations might offer fewer estrogenic side effects, the lowered estrogen dose might leave less leeway for "missed pills," says Rosenberg.

"From a clinical perspective, we are going to have to make sure that women know how to use these pills well, that they are counseled well, and that we follow up with them well," he observes.

Rundell gives her patients verbal and written instructions on proper pill use, risks, benefits, side effects, and timing of pill taking. "I especially emphasize timing on 20 mcg pills, as well as minipills, to help control breakthrough bleeding and improve effectiveness," she states.

Reference

1. Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives: A randomized trial of 20 mcg and 35 mcg estrogen preparations. *Contraception* 1999; 60:321-329. ■

Teens' contraceptive use marked by inconsistency

Good news: More teens are delaying sex, and those who choose to have sex are using contraception at first intercourse. Bad news: The percentage of teen females who used contraception the last time they had sex dropped from 77% in 1988 to 69% in 1995, according to just-released figures from Child Trends, a Washington, DC-based nonprofit nonpartisan research center that studies children, youth, and families.[1]

The statistics contained in the new report are a red flag, says **Sarah Brown**, director of the Washington, DC-based National Campaign to Prevent Teen Pregnancy, which released the full report along with three other items dealing with teen contraceptive use:

- *Protection as Prevention: Contraception for Sexually Active Teens*, a review of current research on contraceptive use by teens; programs and services for sexually active teens; and policy issues;
- *The Next Best Thing: Helping Sexually Active Teens Avoid Pregnancy*, a series of suggestions for helping sexually active teens avoid pregnancy;
- *Risky Business, A 2000 Poll: Teens Tell Us What They Really Think of Contraception and Sex*, a nationally representative survey.

"Nearly one-third of teen girls were completely unprotected the last time they had sex, and of those girls, another one-third used contraception inconsistently," she notes. "And while more teens are now using contraception the first time they have sex, they are less likely than in previous years to use contraception the most recent time they have had sex."

Why aren't teens using contraception all the time? Partner pressure, says one of every two teens surveyed by the National Campaign.[2] Drinking and drug use also play a large role, noted more than 50% of the teens. The nationally representative survey questioned 515 teens ages 12 to 17.

While the poll showed that nearly nine of 10 teens believe it's important to use contraception each and every time they have sex, they are not following through in their actions. Brown sees those statistics as an equation for disaster. "Too many teens, boys and girls alike, are still telling us that they don't use contraception because their partner doesn't want to. And the reasons the partners give for not wanting to use birth control are the same as they ever were: 'It doesn't feel as good,' or 'Just this once,' or 'I thought if I brought birth control you would think I was pushy.'"

Data reviewed by the Child Trends researchers shows that almost 20% of teen females reported that they have had sex before age 15, a percentage that has almost doubled since 1988, says **Jennifer Manlove**, PhD, senior research associate. This finding is of concern, since younger teens are less likely to use contraception consistently and are at a greater risk of early pregnancy or sexually transmitted diseases, she notes. "Teens who report that they are the youngest up for sex are more likely to report that that encounter was nonvoluntary."

Hispanic teens are at particular risk for unplanned pregnancy, according to the Child Trends findings. The percentage of Hispanic teens who are sexually experienced increased from 49% in 1988 to 55% in 1995, while percentages for other ethnic groups declined, researchers note.

"Hispanic teens are least likely to use contraception either at first sex or at most recent sex," notes Manlove. "This group showed the greatest declines in contraceptive use at most recent sex."

Providing contraceptive services to sexually active adolescents remains controversial in the United States, says **Claire Brindis**, DrPH, professor of pediatrics and health policy in the department of pediatrics, division of adolescent medicine and Institute for Health Policy Studies at the University of California, San Francisco school of medicine and the director of the Center for Reproductive Health Policy Research in San Francisco. Brindis is co-author of *Protection as Prevention: Contraception for Sexually Active Teens*.

"Evaluations of programs that offer contraceptive information and services to adolescents consistently demonstrate no evidence that they encourage teens to increase sexual activity or to initiate sexual intercourse earlier than they otherwise would have done," states Brindis. "In addition,

EXECUTIVE SUMMARY

A recent report notes a decrease in the percentage of teens who have had sex and an increase in contraceptive use at first sex among teens, but it finds that teens are inconsistent in contraceptive use.

- One in two teens cites pressure from partners as a main reason for not using contraception. More than 50% also say drinking and drugs are the main reasons.
- The report notes that Hispanic and very young teens are at particularly high risk of pregnancy.

RESOURCES

- **National Campaign to Prevent Teen Pregnancy**, 1776 Massachusetts Ave. N.W., Suite 200, Washington, DC 20036. Telephone: (202) 478-8500. To order *The Next Best Thing: Helping Sexually Active Teens Avoid Pregnancy*, *Protection as Prevention: Contraception for Sexually Active Teens*, or *Trends in Sexual Activity and Contraceptive Use Among Teens*, click on "Publications" on www.teenpregnancy.org.
- **Child Trends**, 4301 Connecticut Ave. N.W., Suite 100, Washington, DC 20008. Telephone: (202) 362-5580. Fax: (202) 362-5533. Web: www.childtrends.org. To review the policy brief, *Trends in Sexual Activity and Contraceptive Use Among Teens*, go to the following Web page: www.childtrends.org/r_ac.cfm.

public opinion surveys indicate that although parents and teens clearly prefer that school-age teens not be sexually active, they also agree that those teens who are sexually active should have access to contraception."

It remains challenging to ensure adequate access to contraceptive care, particularly care provided in a confidential and nonjudgmental manner, says Brindis. Once teens initiate contraceptive use, she notes, several factors are needed to ensure effective compliance: basic knowledge about available methods of contraception; skills to use the method correctly; support in using a method, particularly from a partner; ability to afford the method chosen; and motivation to prevent pregnancy and to use contraception effectively and consistently.

"Our first priority should always be to encourage teens to delay sexual activity, to protect their physical health, their emotional health, and their opportunities for the future," Brown says. "However, no matter how much support we give young people to say 'no,' many will still become sexually active." The National Campaign has issued a publication, *The Next Best Thing: Helping Sexually Active Teens Avoid Pregnancy*, to help highlight what it considers some of the most compelling issues in the challenge to convince sexually active teens to use contraception consistently and carefully every time. "In *The Next Best Thing*, we note that access to contraception is necessary but not sufficient. Restricting sexually active teens from having access to contraception would be a mistake, but simply making contraceptive methods available to teens is not enough to motivate them to protect themselves."

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1. Terry E, Manlove J. *Trends in Sexual Activity and Contraceptive Use*. Washington, DC: National Campaign to Prevent Teen Pregnancy; 2000.

2. International Communications Research for National Campaign to Prevent Teen Pregnancy. *Risky Business, A 2000 Poll: Teens Tell Us What They Really Think of Contraception and Sex*. Washington, DC; Feb. 3-6, 2000. ■

CE objectives

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• Identify clinical, legal, or scientific issues related to development and provisions of contraceptive technology or other reproductive services. **(See "Update won't stop Women's Health Initiative," p. 68, and "Push is on for increased microbicide R&D funds," p. 69.)**

• Describe how those issues affect service delivery and note the benefits or problems created in patient care in the participant's practice area.

• Cite practical solutions to problems and integrate information into daily practices, according to advice from nationally recognized family planning experts. **(See "Osteoporosis: Stop the 'bone robber,'" p. 71.)** ■

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