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IN THIS ISSUE

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Research eyes expanded use for intrauterine systems in women

New uses examined for women's health at international symposium

(Editor's note: This article discusses off-label use of the levonorgestrel intrauterine system.)

Consider the many treatment options when presented with the following cases: the perimenopausal woman with prolonged menstrual bleeding due to uterine leiomyomas; the young woman with significant pain from spreading endometriosis; and the mother with menorrhagia. Which options will you choose?

Medicated intrauterine systems (IUS) may represent a treatment choice in each of these conditions, according to new research presented in October 2006 at the Fifth International Symposium on Intrauterine Devices and Systems for Women's Health. Findings presented at the symposium, sponsored by the Population Council in cooperation with the United Nations Population Fund, highlight the number of uses for such intrauterine devices (IUDs) outside contraception, says **Elof Johansson**, MD, PhD, president of the Population Council's Center for Biomedical Research.

EXECUTIVE SUMMARY

New research highlights the number of uses for intrauterine systems (IUS) beyond contraception.

- The progestin-releasing IUS provides effective contraception, reduces menstrual bleeding, and likely reduces menstrual pain in women with uterine fibroids.
- Use of the levonorgestrel IUS may offer an effective approach in treating endometriosis.
- Women moving into the perimenopause may experience menorrhagia or dysfunctional uterine bleeding. Use of the levonorgestrel IUS may help relieve such symptoms.

While the copper IUD (marketed in the United States as the ParaGard IUD, Duramed, a subsidiary of Barr Pharmaceuticals) is the most-used reversible contraceptive in the world, its use in the United States and part of Europe may be low due to misconception of risks, he reports. This fear is unfounded, says Johansson, as research shows there is no increased risk of infections during use.[1]

The levonorgestrel IUS (marketed in the United States as Mirena LNG IUS, Berlex) works by changing the milieu in the cavity of the uterus, explains Johansson. It also inhibits growth of the endometrium, which makes menstrual bleedings small or absent while the cyclic estrogen production in the ovary is intact, he notes.

Use of the LNG IUS is increasing fast in the United States — now more than 1 million users — and there are strong increases in Europe and upward growth in developing countries, Johansson reports. Since anemia is common in developing countries, use of the device would aid in combating the problem, because research has shown the device reduces menstrual blood loss, which results in improvement of the body iron balance and in an increase in hemoglobin concentration.[2]

IUS for fibroids?

The progestin-releasing IUS provides effective contraception, reduces menstrual bleeding, and likely reduces menstrual pain in women with uterine fibroids, says **Andrew Kaunitz**, MD, professor and assistant chair in the Obstetrics and Gynecology Department at the University of Florida Health Science Center/Jacksonville. Kaunitz presented on progestin-releasing intrauterine systems and leiomyoma at the recent Population Council symposium.

Uterine leiomyomas are the most common benign pelvic tumors found in women. Prevalence data varies. Some studies indicate as many as 70% premenopausal women have fibroids.[3]

In a 2003 study, researchers reported a dramatic reduction in menstrual blood loss accompanied by an improvement in hematological indices in patients with uterine leiomyomas who were treated with the LNG IUS for one year.[4] In a study of menorrhagic patients with submucous leiomyomas, researchers found the LNG IUS was as effective as thermal balloon ablation in treating excessive bleeding and related anemia.[5]

There are caveats to device use for uterine fibroids, notes Kaunitz. Long-term symptomatic relief is not guaranteed, and in the case of the levonorgestrel IUS, it is not likely to effectively treat such nonmenstrual fibroid symptoms as pressure. Expulsion rates appear acceptable, but are higher than in women without fibroids, he notes. However, for selected women with symptomatic fibroids seeking treatment, the

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Editorial Questions

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LNG-IUS represents an appropriate option prior to proceeding with surgery, says Kaunitz.

Use of the LNG IUS may offer an effective approach in treating endometriosis, according to research presented at the recent symposium.[6] Endometriosis is defined as the presence of endometrial tissue in abnormal locations such as the ovaries, fallopian tubes, and abdominal cavity. It is estimated that endometriosis affects almost 10% of women of reproductive age; 70%-90% of women with chronic pelvic pain, dysmenorrhea, dyspareunia, infertility or menstrual disturbances have endometriosis.[7]

To evaluate the effectiveness of the LNG IUS in treating endometriosis-related pain, Brazilian researchers conducted a randomized controlled clinical trial using LNG IUS and a gonadotrophin-releasing hormone (GnRH) analogue, the gold standard drug treatment for endometriosis. Eighty-women were enrolled in the six-month trial.

Both the LNG IUS and the GnRH analogue were effective in the treatment of chronic pelvic pain associated with endometriosis, although no differences were observed between the two treatments. Since the LNG IUS does not provoke hypoestrogenism and only requires one medical intervention for its introduction every five years, the device may represent an effective option for endometriosis treatment, the researchers conclude.[8]

Look at options

Women moving into the perimenopause may experience menorrhagia or dysfunctional uterine bleeding. When they reach menopause, some women who choose combined hormone therapy may experience bleeding/spotting due to use of continuous progestin for endometrium suppression.[9] The LNG-IUS may aid in relieving these problems in peri- and postmenopausal women.[9]

What are some of the benefits of use on the LNG-IUS in the perimenopause? The device prevents ovulation, which is important for those women who continue to have ovulations prior to menopause, says **Régine Sitruk-Ware**, MD, executive director of the Population Council's Product Research and Development Division. It also protects the endometrium from overproliferation, states Sitruk-Ware, who presented on use of the device in postmenopausal women at the symposium.[10]

"In the perimenopause, high secretion of estradiol from the ovaries is still possible and there are very few ovulations, hence very low levels of progesterone to oppose the proliferative effects of estrogen on the endometrium," she notes. "Therefore, the progestin contained in the IUS and delivered directly into the uterine cavity compensates for that lack of progesterone and prevents the excessive stimulation of the tissue by the estrogen."

Women in the perimenopause who experience dysfunction bleeding may look to hysterectomy for relief. A new systematic review of scientific studies indicates that while use of conservative surgery reduces blood loss more than the IUS, the two treatments appear about equal in terms of patient satisfaction.[11] ***(Contraceptive Technology Update* reported on the review in its August 2006 article, "Look at LNG IUS for menorrhagia treatment," p. 89.)**

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Providers in swing with Implanon training

Your patient is a 29-year-old mother of three active young children. She has had limited success with using birth control pills and says that the daily dosing schedule is a challenge. She shakes her head "no" to the contraceptive patch and vaginal ring, and she doesn't want to limit her options with the choice of tubal sterilization.

What is your next step in contraceptive counseling?

U.S. providers are undergoing training to offer the single-rod contraceptive implant Implanon, marketed by Organon of Roseland, NJ, and Oss, the Netherlands. Approved by the Food and Drug Administration (FDA) in July 2006, Implanon releases a continuous low, steady dose of the progestin etonogestrel for up to three years. The average hormone release rate is 40 mcg per day. The device, which is about the size of a matchstick, is inserted subdermally just beneath the skin on the inner side of a woman's upper arm during an in-office procedure. ***(Contraceptive Technology Update* reported on the implant's approval in the September 2006 article, "Bulletin: Single-rod contraceptive implant Implanon gets Food & Drug Administration's OK," p. 97.)**

Faculty training began as soon as the FDA approval was in hand, reports **Frances DeSena**, company spokeswoman. Physicians in the faculty program are beginning the next wave of education by training physicians in off-site programs around the country, she notes. Providers who are interested in undergoing training can register by calling a toll-free number, (877) 467-5266, or visiting the product web site, www.implanon-usa.com. (Click on "Healthcare Provider," then enter your name, professional designation, specialty, and state license number.)

Company-sponsored training is key. Providers cannot write prescriptions for the implant until they undergo the instructional process and such training is properly documented, says **Paul Fine**, MD, a member of the physician faculty. Fine, an associate professor of gynecology at Baylor College of Medicine in Houston, also serves as medical director for Planned Parenthood of Houston and Southeast Texas. "I think Organon is doing this in a very structured and wise way to make sure that everybody who is trained inserts it the same way, with the same guidelines and the same technique," explains Fine. "They also are given the same information that matches the FDA patient brochure and the data on which the approval was based."

What is involved?

While U.S. providers are just beginning to work with the device, clinicians on the international front have had years of experience with the one-rod implant. Organon launched Implanon in 1998 following 12 years of research, with Indonesia as the first country to approve the device. Since that time, more than 40 European and Asian countries have approved its use.[1]

U.S. providers must undergo a three-hour instructional program, which includes a didactic slide presentation that covers data about the implant, as well as a training session using realistic model arms, says Fine. Faculty presenters supervise trainees in the correct insertion technique and demonstrate proper use of the insertion device. They also cover removal techniques and instructions on necessary documentation. "When done correctly, it is extremely safe, it is technically very easy, and I think it will be an excellent addition to a woman's choice for long-term effective contraception," states Fine.

While Implanon is approved in the United States for three years of use, research indicates its contraceptive effect may last at least four years.[2,3] In clinical trials, no women became pregnant over the 5,000 woman-years of study.[4,5] The implant can be removed at any time, after which fertility is rapidly restored to pre-implant status.

Implanon is particularly good for women with

EXECUTIVE SUMMARY

U.S. providers are undergoing training to offer the single-rod contraceptive implant Implanon, marketed by Organon. Implanon releases a continuous low, steady dose of the progestin etonogestrel for up to three years. The average hormone release rate is 40 mcg per day.

- Providers must undergo training prior to prescribing the contraceptive implant. To sign up for training, providers can visit the product web site (www.implanon-usa.com) or dial a toll-free number [(877) 467-5266].
- As with all progestin-only methods, irregular bleeding is a common occurrence with Implanon. To ensure patient satisfaction with the method, women need to be counseled to expect changes in their menstrual cycles.

contraindications to or side effects from estrogen.[6] However, as with all progestin-only methods, irregular bleeding is a common occurrence. To ensure patient satisfaction with the method, women need to be counseled to expect changes in their menstrual cycle. According to the patient information insert, one in 10 women in Implanon studies discontinued method use due to bleeding problems.[7]

Tell women to expect that their menstrual periods will be irregular and unpredictable throughout the time Implanon is in place, the patient packaging advises. Women may have more bleeding, less bleeding, or no bleeding. The time between periods may vary, and in between periods, spotting may occur.

"The biggest downside, and counseling is important, is that the bleeding pattern can be totally unpredictable, so that a woman almost needs to have a panty liner or tampon in her purse, because you can't predict it — but that is where counseling comes in," says Fine. "Many women are willing to trade that for a very effective method of contraception that they don't have to think about."

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Shipment of dual-label EC now reaching stores

Access to emergency contraception (EC) has been expanded. Shipments of the new dual-label version of Plan B, the levonorgestrel-only EC drug, are now hitting pharmacy market shelves.

Shipments of the drug began in early November 2006. The dual-label product, approved in August 2006 by the Food and Drug Administration (FDA), is available "behind the counter" — but without a prescription — to consumers 18 years of age and older, and it remains prescription-only for women 17 and younger. ***(Contraceptive Technology Update* reported on the FDA approval in its October 2006 article, "Finally! Emergency contraception given approval by FDA for nonprescription sale," p. 109.)** The new dual-label drug replaces the Plan B prescription-only product that had been marketed in the United States since 1999. Since Plan B remains a prescription product for women 17 and younger, it is being sold only in retail pharmacies under the supervision of a pharmacist.

Nine states — Alaska, California, Hawaii, New Mexico, Maine, Massachusetts, New Hampshire, Vermont, and Washington — have pharmacy access programs, which enable women to get Plan B directly from participating pharmacists without going to a prescriber first. Women younger than age 18 in these states still will be able to access Plan B directly from a pharmacist. Those under age 14 in Hawaii need parental consent to get Plan B through a pharmacist.[1]

Barr Pharmaceuticals of Woodcliff Lake, NJ, is moving on several fronts to educate providers and consumers about the drug, says **Carol Cox**, company spokeswoman. To prepare pharmacists, Cox says the company has issued faxes with information about how to dispense the product, an update regarding its new packaging, and a reminder that government-issued identification must be shown for proof of age in order to purchase the drug behind the counter. The company is offering continuing education programs for

EXECUTIVE SUMMARY

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- Nine states have pharmacy access programs, which enable women to get Plan B directly from participating pharmacists without going to a prescriber first. Women younger than age 18 in these states still will be able to access Plan B directly from a pharmacist. Those under age 14 in Hawaii need parental consent to get Plan B through a pharmacist.

pharmacists and is working with chain drug stores and pharmacist trade associations to educate their employees/members, Cox reports.

Duramed Pharmaceuticals, the Barr subsidiary which distributes Plan B, is launching its Convenient Access Responsible Education (CARE) Program, a comprehensive education program for health care professionals and consumers to clear up confusion about the dual-status drug. "The company is undertaking a direct to consumer print campaign in women's magazines aimed at women 18 and over regarding the availability of the new product," states Cox. "We also host a web site, www.Go2PlanB.com, where women and health care providers can get information regarding the product."

Check revamped EC site

Those looking for information and direction on emergency contraception should check out the recently revamped EC web site, www.Not-2-Late.com. Established in 1994 by **James Trussell**, PhD, *Contraceptive Technology* co-author and professor of economics and public affairs and director of the Office of Population Research at Princeton (NJ) University, the site was one of the first on the Internet to offer women information on the method. It is managed and operated by the Office of Population Research and the Association of Reproductive Health Professionals (ARHP).

The revised site features an improved menu structure, expanded content, and video testimonials from women who have used EC. It also provides information for pharmacists, many of whom will find themselves in a new role of consumer counselors regarding emergency contraception. Funding for the site update was provided by the Hewlett Foundation of Menlo Park, CA.

The web site works to increase women's knowledge about and timely access to emergency contraception and other reproductive health choices, both in the United States and abroad. To continue in that focus, it offers EC information, derived from medical literature, in English, Spanish, French, and Arabic, as well as a searchable database of EC providers in the United States and a searchable database of EC pills in every country.

Family planning providers will continue to play an important role when it comes to emergency contraception, says **Vanessa Cullins**, MD, MPH, vice president for medical affairs at Planned Parenthood Federation of America in New York City. Planned Parenthood affiliates are one of the single largest providers of EC, she says.

"We have gotten to that place because of all the work affiliates do within their local communities to increase awareness and access to emergency contraception," states Cullins. "Our web site, [www.plannedparenthood.org], contains information about emergency contraception, and most definitely, the over-the-counter status for women who are 18 and older."

A number of Planned Parenthood affiliates have had "Free EC" days to raise awareness about emergency contraception, and the federation is considering a simultaneous nationwide event, says Cullins. (Grass-roots organizers also are broadening access through the web site, www.emergencykindness.net, where women can receive Plan B within 24 hours and at no cost.)

"We will continue to try to both increase awareness of about emergency contraception, about how to use it, and how important it is to have emergency contraception on hand in the event of a contraceptive mishap or accident," Cullins states. "I think all health care providers should continue to stock emergency contraception, and if they haven't stocked emergency contraception in the past, they should definitely consider it."

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Research emerges on continuous regimen OC

When using contraception to delay or stop menstrual periods, return to fertility is important to patients. Results of a national survey indicate 58% of women worry that menstrual suppression will affect their ability to have children.[1] New research on a continuous-regimen oral contraceptive (OC) under review at the Food and Drug Administration (FDA) suggests that the drug's return to fertility is comparable to rates observed with cyclic combined pills.[2]

The research was presented at the annual meeting of the American Society for Reproductive Medicine.

Lybrel (20 mcg ethinyl estradiol/90 mcg levonorgestrel tablets) is a low dose, continuous,

EXECUTIVE SUMMARY

New research indicates that return to fertility rates for Lybrel, a continuous-regimen oral contraceptive under review at the Food and Drug Administration (FDA), are comparable to rates observed with cyclic combined pills.

- When it comes to using contraception to delay or stop menstrual periods, return to fertility is an important issue in patients' decision process. Results of a national survey indicate 58% of women worry that menstrual suppression will affect their ability to have children in the future.
- Lybrel was given approvable status by the FDA in June 2006. The company is submitting additional manufacturing stability data and further analyses of submitted clinical data to gain full regulatory approval.

noncyclic combination oral contraceptive under development by Wyeth. The drug was given approvable status by the FDA in June 2006. The company is submitting additional manufacturing stability data and further analyses of submitted clinical data to gain full regulatory approval of the drug. ***(Contraceptive Technology Update* reported on Lybrel in the August 2006 article, "New pill options give women choices while changing menstrual bleeding," p. 85.)** If given final approval, Lybrel will be the only combination oral contraceptive approved with this regimen designed to be taken daily, 365 days a year, without a placebo phase or pill-free interval.

Women are now familiar with extended-regimen contraception due to dedicated products such as Seasonale (0.03 mg ethinyl estradiol/0.15 mg levonorgestrel tablets) and Seasonique (0.03 mg ethinyl estradiol tablets /0.15 mg levonorgestrel and 0.01 mg ethinyl estradiol tablets), both marketed by Duramed, a subsidiary of Barr Pharmaceuticals. Lybrel is in a slightly new paradigm, says **Kurt Barnhart**, MD, director of clinical research and associate professor of OB/GYN at the University of Pennsylvania Medical Center in Philadelphia. Barnhart served as lead author on the recently presented Lybrel research.

"The fact that you can use oral contraceptive pills continuously for up to a year is relatively new, and therefore, whenever a product is launched that is new, you want to have very good reassurance of its function and safety," Barnhart says. "One of the theoretical concerns was a delayed return to fertility, and I think the data that we presented can reassure clinicians that that is not an issue, that there will be no delay of fertility."

To evaluate the return to fertility among women planning to become pregnant after the use of Lybrel, researchers followed 21 women for up to 12 months following their last dose of treatment. Average duration of treatment with the drug was 197 days within the study group. The pregnancy rate was 57% (12/21) at three months and 81% (17/21) at 12 months after discontinuation, the scientists report. After the 12-month post-study follow-up, information was sought for the remaining four women who had not become pregnant. One woman conceived within 14 months of the last treatment for a total pregnancy rate of 86% (18/21). In the remaining three women who did not conceive, one woman ceased trying to become pregnant by 12 months, and the other two were lost to follow-up after 12 months, note the researchers.[2] Eighteen pregnancies resulted in 17 live births and one spontaneous abortion. Data were obtained from 10 of the 17 newborns; all were uncomplicated term deliveries.[2]

Research explores safety issues

Is extended menstrual suppression safe? Research findings are encouraging. Both the one-year investigation of Seasonale and a six-month trial of continuous use of a 20 mg ethinyl estradiol/100 mg levonorgestrel OC indicate no untoward effects on the endometrium.[3,4]

What are the potential disadvantages? Patient counseling should include the following[5]:

- Breakthrough bleeding initially is more common than with conventional OCs.
- It often takes a few months before the desired effect of reduced bleeding is achieved.
- With no monthly withdrawal bleed, it may be more difficult for patients to determine pregnancy. Breast tenderness, nausea, and fatigue may signal pregnancy in women using extended regimens. **(See resource box on p. 8 to obtain more information on extended/continuous regimens.)**

In addition to eliminating the monthly withdrawal bleed, a continuous regimen pill may offer other noncontraceptive benefits as well. Results of a 2005 study indicate that Lybrel significantly alleviates cycle-related symptoms.[6] During the three-month, open-label substudy, participants with a history of cycle-related symptoms or premenstrual syndrome (PMS) reported a decrease in symptoms compared to baseline by the first pill pack, and continued to report a decrease in symptoms during the two subsequent pill packs.[5] **(To read more**

RESOURCE

Get more information on extended/continuous regimens of contraception. Visit the Menstruation Resource Center portion of the web site for the Association of Reproductive Health Professionals (ARHP), www.arhp.org. Click on "Resources" and then "Menstruation Resource Center" to access articles on the subject as well as patient information, such as an interactive tool on menstrual suppression developed by the organization.

about the study, see the article, "Continuous regimen OCs: Will U.S. see new pill?" January 2006 *Contraceptive Technology Update*, p. 4.)

Both mood and physical symptoms of PMS improved with daily continuous levonorgestrel, says **Ellen Freeman**, PhD, professor of obstetrics and gynecology at the University of Pennsylvania in Philadelphia and lead author of the study. "This may be an appropriate option for cycle-related symptom relief, particularly for women who also want contraception," Freeman says.

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Review the options for premenstrual syndrome

When is "that time of month" a problem for some women? When symptoms such as depression, wide mood swings, breast tenderness, or muscle pain enter into the picture, a diagnosis of premenstrual syndrome (PMS) may be in order. However, when symptoms are more severe, clinicians may consider a diagnosis of premenstrual dysphoric disorder (PMDD).

For a PMDD diagnosis, the patient must have:

- five or more of the following symptoms during most menstrual cycles in the past year: irritability, tension, depressed mood, mood swings, decreased interest in usual activities, difficulty concentrating, lethargy, marked change in appetite, insomnia or hypersomnia, sense of being overwhelmed, and physical symptoms such as breast tenderness and bloating. One or more of these symptoms must be depressed mood, tension, mood swings, or irritability;
- a disturbance that significantly interferes with social or occupational functioning;
- symptoms that are not an exacerbation of another disorder, such as major depressive disorder.[1] **(For more on the distinction between PMS and PMDD, see "The Pill for PMS relief? New research says yes," May 2003 *Contraceptive Technology Update*, p. 52.)**

The Food and Drug Administration (FDA) has just given approval to use of Yaz (Berlex; Montville, NJ), an oral contraceptive with 24 days of active hormones and four days of placebo pills, for the

EXECUTIVE SUMMARY

Premenstrual syndrome, characterized by such symptoms as depression, wide mood swings, and breast tenderness, can be challenging for women. However, when symptoms are more severe, a diagnosis of premenstrual dysphoric disorder (PMDD) may be in order.

- For a PMDD diagnosis, the patient must have five or more of the following symptoms during most menstrual cycles in the past year: irritability, tension, depressed mood, mood swings, decreased interest in usual activities, difficulty concentrating, lethargy, marked change in appetite, insomnia or hypersomnia, sense of being overwhelmed, and physical symptoms such as breast tenderness and bloating. One or more of these symptoms must be depressed mood, tension, mood swings, or irritability.
- The Food and Drug Administration has approved an indication for treatment of PMDD symptoms to Yaz, an oral contraceptive.

treatment of emotional and physical symptoms of PMDD. The drug was approved for contraceptive use in March 2006. ***(CTU* reported on the approval in its article, "Shortening the pill-free interval: new contraceptives take next step," May 2006, p. 49.)** How will the new indication aid health care providers?

"In the past, most clinicians treated women with PMS, severe PMS, and even those with PMDD, with oral contraceptives; in general, they were not effective," observes **Andrea Rapkin**, MD, professor of obstetrics and gynecology at the David Geffen School of Medicine at the University of California Los Angeles (UCLA). "So now there is a situation where something that comes naturally to an OB/GYN [prescribing an oral contraceptive) will actually in certain cases — the response rate is probably in the 60-65% range— be effective for PMDD."

In a clinical trial of Yaz, 64 women were randomized to the study drug or placebo for three cycles; after a washout period of one treatment-free cycle, they were switched to the alternate treatment.[2] Researchers report the mean decrease from baseline for total Daily Record of Severity of Problems scores while using Yaz was significantly greater than for placebo (-12.47, 95% CI= -18.28, -6.66; p< .001). A positive response was recorded in 61.7% and 31.8% of subjects while taking the study drug and placebo, respectively (p=.009), researchers report.[2]

Look at progesterone

For women with PMS, some clinicians have looked to progesterone therapy for relief of symptoms. Such treatment has been based on the hypothesis that the ratio of progesterone and its derivatives in women with PMS is lower than that found in women without the syndrome.[3]

A new review of the current research on progesterone therapy indicates there is only a little good evidence for treating premenstrual syndrome with progesterone.[4] While reviewers found some evidence for relief with progesterone in the included studies, they determined that the trials differed in route of administration, dose, duration of treatment and selection of participants. With such variations in study design, the outcomes differed, they report.[4]

If women are treated with progesterone for PMS, they should be counseled about possible changes in cycle length and sedative effects, the reviewers note. Women who have considered themselves infertile could conceive when treated with progesterone for PMS They should be advised about contraceptive options if pregnancy is not wanted, the reviewers state.

Better study design is needed to more completely capture the impact of progesterone on PMS, says **Olive Ford**, who served as lead author for the review. Ford is the former honorary research officer for the National Association for Premenstrual Syndrome, a British-based organization.

"My own experience with women in self-help groups and answering the National Association for Premenstrual Syndrome telephone helpline suggests that women may have little help with two 400 mg suppositories daily, but have complete relief with three or four," states Ford. "If they were participants in one of the clinical trials reviewed, their data would be negative."

SSRIs as option?

Selective serotonin reuptake inhibitors (SSRIs) represent another therapy for premenstrual syndrome. Standard SSRIs include fluoxetine (Prozac, Sarafem, both from Eli Lilly of Indianapolis), sertraline (Zoloft, Pfizer, New York City), paroxetine (Paxil CR, GlaxoSmithKline, Philadelphia), and escitalopram (Lexapro, Forest Laboratories, New York City). The FDA has approved indications for Sarafem and Paxil CR for treatment of PMDD symptoms.

According to a recent review of current research, there is now very good evidence to support the use of selective serotonin reuptake inhibitors in the management of severe premenstrual syndrome.[5]

Reviewers included 15 trials in the systematic review, with 10 trials examined in the main analyses. SSRIs were found to be highly effective in treating premenstrual symptoms, the reviewers concluded. Secondary analysis showed the drugs were effective in treating physical and behavioral symptoms.[5]

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Update practice on osteoporosis prevention

The next patient in your exam room is in her mid-40s. She notes that her last monthly period was 11 months ago. She continues to use condoms for pregnancy prevention. She has a thin body and a small bone frame, and she smokes 15-20 cigarettes a day. Her medical history indicates a family history of osteoporosis. What is your next move?

Consider use of bone mineral density (BMD) testing for osteoporosis. While routine BMD testing is not recommended for healthy reproductive-age women, testing is appropriate for postmenopausal women older than age 40 who present with other risk factors for fractures.[1]

Osteoporosis is a key concern for women, particularly as they age. Some 10 million Americans — 80% who are women — have osteoporosis, according to the National Institutes of Health's Osteoporosis and Related Bone Diseases National Resource Center.[2] The center estimates that an additional 34 million Americans have low bone mass (osteopenia), placing them at increased risk for osteoporosis and related fractures. One in two women and one in four men older than age 50 can expect to have an osteoporosis-related fracture in their lifetime, according to the center's statistics.[2]

Risk factors for osteoporosis include: low estrogen levels due to missing menstrual periods or menopause, anorexia nervosa, diet low in calcium and vitamin D intake, long-term use of oral steroids, lack of exercise, smoking, and alcohol use.[2] Guidance issued by the World Health Initiative (WHO) defines osteoporosis in women as a BMD value at least -2.5 Standard Deviation (SD) below the mean value of a young healthy population (T-score $\leq$ -2.5).[3]

Get ready for updated WHO guidance that will target clinical risk factors in addition to bone mineral density measurements to improve prediction of fracture, says **Douglas Bauer**, MD, associate professor of medicine, epidemiology, and biostatistics at the University of California San Francisco (UCSF) School of Medicine. The most immediate impact of the WHO report will be a better understanding of the relationship between BMD, risk factors, and the 10-year probability of fracture, says Bauer, who provided an overview at a July 2006 osteoporosis conference sponsored by the university.[4] The guidance is expected to be published in 2007. *(Editor's note: Watch upcoming issues of* Contraceptive Technology Update *for coverage.)*

"This should help clinicians discuss the risks and benefits of various treatment options, including treatment and watchful waiting," says Bauer. "Eventually the WHO models will be used to construct regional cost-effectiveness models, which might be incorporated into clinical guidelines and influence reimbursement."

What can clinicians do to help patients prevent osteoporosis? Advocate prevention strategies such as: eating a diet rich in calcium and vitamin D, exercising, smoking cessation, and avoidance of excessive alcohol intake.[2] Women ages 19-50 should get a daily intake of 1,000 mg of calcium and 200 IU of vitamin D to keep bones strong.[2]

Medical treatment to reduce risk of fracture should be considered if a woman's BMD is above –2.5 with other risk factors present, such as family history of fracture, a personal history of fracture, low body mass index, smoking, or high bone

EXECUTIVE SUMMARY

Osteoporosis, a condition characterized by low bone mass and structural deterioration of bone tissue, is a key concern for women, particularly as they age. Some 10 million Americans — 80% of whom are women — have osteoporosis.

- Get ready for updated international guidance that will target clinical risk factors and bone mineral density measurements to improve prediction of fracture associated with osteoporosis.
- Advocate prevention strategies such as eating a diet rich in calcium and vitamin D, exercising, stopping smoking, and avoiding excessive alcohol intake.

COMING IN FUTURE MONTHS

- Banish myths, misconceptions about OC safety and efficacy
- Review treatment options for acute uterine bleeding
- How to ensure more consistent use of OCs
- Get counseling tips for providing vaginal contraceptive ring
- Polycystic ovary syndrome: Understand the complexities

turnover.[1] Family planning clinicians may be most familiar with estrogen-based drug therapies. These include Climara (Berlex Laboratories; Wayne, NJ); Estrace (Warner Chilcott; Rockaway, NJ); Premarin and Prempro (both from Wyeth; Philadelphia), and Estraderm and Vivelle-Dot (both from Novartis Pharmaceuticals; New York City).[5]

The Women's Health Initiative (WHI) study showed that estrogen/progesterone significantly reduced the risk of hip and vertebral fractures.[6] Because the WHI also showed increased risk of vascular side effects and breast cancer,[7] estrogen has become a smaller part of osteoporosis prevention and therapy, says **Deborah Sellmeyer**, MD, an endocrinologist and assistant professor of medicine in residence at UCSF. Its current use centers mostly in the perimenopause and immediate postmenopausal periods for women to relieve such symptoms as hot flashes, observes Sellmeyer, who serves as director of the UCSF/Mount Zion Osteoporosis Center.

What is the role of low-dose and ultra-low dose estrogen formulations in osteoporosis prevention strategies? One example of such therapy is Menostar, a transdermal system from Berlex. Approved by the Food and Drug Administration (FDA in 2004, it delivers 14 mcg of estradiol a day, the lowest dose of products approved for post-menopausal osteoporosis prevention.

Subsequent studies have shown that half the estrogen dose used in the WHI can increase bone density,[8] but no fracture data are yet available on any doses or formulations other than the one used in the WHI, says Sellmeyer. No vascular side effects were seen in the studies that looked at low-dose estrogen for bone density, but these studies were much smaller than the WHI, notes Sellmeyer.

Research indicates that low-dose estrogen can increase bone density and help alleviate symptoms of menopause; whether it can prevent fractures is unknown, and whether there is any increased risk of breast cancer or vascular side effects is unknown, Sellmeyer points out. Women and their providers

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the articles, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers and refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity with the **June** issue, you must complete the evaluation form provided and return it in the reply envelope provided in that issue to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

CE/CME Questions

After reading *Contraceptive Technology Update*, the participant will be able to:

- **Identify** clinical, legal, or scientific issues related to development and provisions of contraceptive technology or other reproductive services.
- **Describe** how those issues affect services and patient care.
- **Integrate** practical solutions to problems and information into daily practices, according to advice from nationally recognized family planning experts.

1. What is the gold standard treatment for endometriosis?

A. gonadotrophin-releasing hormone (GnRH) analogue
B. Tricyclic antidepressants
C. Thermal balloon ablation
D. Diuretics

2. How big is the contraceptive implant Implanon?

A. 4 inches in length
B. About the size of a matchstick — 4 cm in length
C. 6 inches in length
D. 12 inches in length

3. What is the brand name of the oral contraceptive that has an approved indication for treatment of premenstrual dysphoric disorder symptoms?

A. Ortho Tri-Cyclen Lo
B. Seasonale
C. Yaz
D. Alesse

4. Which of the following drugs is an example of ultra-low dose estrogen formulations in osteoporosis prevention?

A. Lexapro
B. Prempro
C. Sarafem
D. Menostar

Answers: 1. A; 2. B; 3. C; 4. D.

must weigh the risks and potential benefits in using these therapies, she notes.

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Contraceptive Technology Update *is endorsed by the National Association of Nurse Practitioners in Women's Health and the Association of Reproductive Health Professionals as a vital information source for health care professionals.*

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S·T·D QUARTERLY™

Family planning providers get in gear to offer new HPV vaccine to young women

Vaccine addition to federal immunization program broadens access

Access to Gardasil (Merck & Co., Whitehouse Station, NJ) continues to expand as the shot has been added to the federal Vaccines for Children (VFC) program for young women ages 9 to 18. The program is administered at the national level by the Centers for Disease Control and Prevention (CDC) through its National Immunization Program.

"The Vaccines for Children Program provides a tremendous safety net for the most impoverished and for special vulnerable groups in the country," explains **Anne Schuchat**, MD, director of the CDC's National Center for Immunization and Respiratory Diseases. Any young woman who is eligible for the Vaccines for Children program will have access to the vaccine, she notes.

WellPoint in Indianapolis, America's largest health insurer, announced that it would cover costs for the new vaccine following regulatory approval and recommendation for vaccine use by the CDC's Advisory Committee on Immunization program (ACIP) in June 2006. ***(Contraceptive Technology Update* reported on the ACIP recommendation in its article, "HPV vaccine, with nod from FDA, is first one approved to prevent cervical cancer," September 2006, p. 97.)** While Merck reports more than 95 insurance plans have decided to reimburse costs for Gardasil, cost has been a factor for patients without insurance coverage. At $120 a dose, plus provider charges, a full three-shot series can run $400 to $500.[1]

EXECUTIVE SUMMARY

Gardasil, the cervical cancer vaccine, has been added to the federal Vaccines for Children for young women ages 9 to 18.

- Inclusion in the federal subsidized program will expand access to the vaccine, as will a separate program sponsored by the vaccine's manufacturer that is designed for women ages 19 and older.
- While more than 95 insurance plans have decided to reimburse costs for Gardasil, cost has been a factor for patients without insurance coverage. At $120 a dose, plus provider charges, a full three-shot series can run $400 to $500.

Program adds coverage

To further broaden access to the vaccine, Merck has initiated a new patient assistance program. Currently available in private physicians' offices, the program allows Gardasil and other proprietary vaccines to be provided free of charge to those ages 19 and older who are uninsured and who are unable to afford vaccines.

Patients may be eligible for the program if all three of the following conditions apply:

- United States resident, age 19 or older;
- no health insurance coverage (examples of coverage include private insurance, health maintenance organization, preferred provider organization, college health plan, Medicaid, veterans' assistance, or any other social service

agency support);

• household income less than $19,600 for individuals, $26,400 for couples, or $40,000 for a family of four.

Individuals who do not meet these criteria still may qualify for the vaccine program if the patient has special circumstances of financial and medical hardship. Upper-income limit for exceptional patients is $39,200 for individuals, $52,800 for couples, and $80,000 for a family of four. **(See the resource box on p. 3 for enrollment information.)**

Merck will use the following criteria to determine licensed prescriber participation:

• stocks Merck vaccines;

• does not purchase vaccines for Merck Vaccine Patient Assistance Program-eligible population with government funds;

• willing to screen applications according to Merck's eligibility criteria and to work with Merck's vendor to process applicants;

• willing to accept potential auditing to participate in the program and that no vaccine administration fee is provided by Merck;

• willing to keep individual immunization records.

Will nonprofit clinics be eligible to participate in the program? The answer is a qualified "yes." Practices that are wholly owned and operated by the government are not eligible for the program at this time, states the corporate web site.

A nonprofit organization, the Partnership to End Cervical Cancer, is advocating to make cervical cancer vaccines part of routine preventive health care for American women. More than 20 member organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the Planned Parenthood Federation of America, have joined the organization, which is focused on educating women about cervical cancer and encouraging the public health network, providers, and policy-makers to take action to make sure women have access to vaccines against the disease. GlaxoSmithKline of Research Triangle Park, NC, plans to seek regulatory approval in 2007 for its HPV vaccine, Cervarix. The bivalent vaccine is formulated to strike HPV types 16 and 18. **(See the article, "Immunization schedule may soon grow, HPV vaccine under regulatory review," July 2006 *STD Quarterly* supplement, p. 1.)**

Help put use of the vaccine into practice in your facility: Look to new clinical recommendations released from ACOG.[2] The new committee opinion offers general information about the vaccine and provides guidance on proper administration, precautions, and contraindications.

Obstetrician-gynecologists should be proactive in educating patients about the vaccine so that as many women as possible are able to take advantage of it, says **Douglas Laube**, MD, MEd, ACOG president Providers must be prepared to administer the vaccine and to answer patient and parent questions that will arise, he notes.

While use of the vaccine is important, recommendations for cervical cytology screening remain unchanged, the ACOG guidelines emphasize. Pap screening should begin within three years of sexual intercourse (or by age 21) and then annually until age 30. After age 30, most women can continue annual testing or can choose to be tested every two to three years after three consecutive negative Pap tests, the guidance notes.[2]

While the Gardasil vaccine protects against human papillomavirus (HPV) types 6, 11, 16, and 18, there are additional HPV strains that can cause cervical cancer. Pap testing can detect abnormal cervical cells caused by other HPV strains not covered by the vaccine, the guidance states.

Who should get shots?

Gardasil is a ready-to-use, three-dose, intramuscular vaccine. According to its prescribing information, it should be administered in three intramuscular injections in the upper arm or upper thigh over six months.[3] The recommended dosing schedule is to give the first dose, followed by the second dose two months after the initial injection, with the third dose administered six months after the initial dose.

While the Food and Drug Administration has approved the vaccine for girls and women ages 9 to 26, ACIP recommendations advise that vaccine administration begin between the ages 11 and 12. Vaccination also is recommended for women up to age 26, regardless of sexual activity.

Women who previously have had abnormal cervical cytology, genital warts, or precancerous lesions can be vaccinated. Those with suppressed immune systems also can be vaccinated, although the protection may be less than those with normal immune function.

Advise patients that the HPV vaccine is not a treatment for current HPV infection or genital warts. Women who are undergoing treatment for

RESOURCE

To learn more about Merck & Co. Vaccine Patient Assistance Program, go to the corporate web site, www.merck.com. Click on "Patient Assistance Program," then under the subheading "Merck Vaccine Patient Assistance Program," click on "Learn More." Application forms in English and Spanish are available. Licensed prescribers and their office personnel also can call (800) 293-3881 to obtain enrollment applications for patients and to request additional information about the program.

HPV-related symptoms such as cervical cytology abnormalities or genital warts should continue taking their prescribed medication while going through the immunization process.

While Gardasil has not been shown to have a harmful effect on pregnancy, it is not recommended that pregnant women be vaccinated with the drug. If a woman discovers she is pregnant during the vaccine schedule, she should delay finishing the series until after she gives birth. Women who are breast-feeding can receive the vaccine, the prescribing information states.[3]

Reproductive health professionals have played a vital role in preventing morbidity and mortality from HPV-related disease through the provision of education, prevention, and treatment, states **Evan Myers**, MD, MPH, associate professor of OB/GYN at Duke University Medical Center in Durham in a recent published editorial on vaccination.[4] Providers can continue such efforts by offering vaccination to appropriate populations, continuing to educate patients on other effective methods for prevention of HPV-related diseases, and advocating for policies to ensure maximum access and coverage, he states.

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Reinfection is common after STD treatment

You have just written a prescription for an adolescent female to treat a chlamydial infection. When you close her file, what are the chances it will reappear in your inbox in the next month or two?

The probability is high. While antibiotic treatment is effective in curing sexually transmitted diseases (STDs), reinfection is common, according to results of a new study.[1]

To find out how frequently reinfection occurs in the year following treatment, researchers tracked 2,419 men and women who were participating in a large study of HIV prevention counseling. After an initial examination, participants returned every three months over the next year, where they underwent STD testing and were questioned about symptoms and sexual activity since their last visit.

During the study, 26% of the women and 15% men had at least one new STD infection. Many of the participants who developed new infections had no symptoms and were unaware that they were infected again until they were told of the test results.[1]

It is very important that clinicians stress the need for rescreening following treatment for such infections as chlamydia and gonorrhea because these persons are at high risk for new asymptomatic infections that would go undetected without rescreening, says **Thomas Peterman**, MD, MSc, an

EXECUTIVE SUMMARY

Reinfection is common following treatment of sexually transmitted diseases (STDs), according to results of a new study.

- During the study, 26% of the women and 15% men had at least one new STD infection. Many of the participants who developed new infections had no symptoms and were unaware that they were infected again until they were told of the test results.
- The Centers for Disease Control and Prevention is working in Washington, DC, New York City, and San Diego to examine rescreening in STD clinics. Stemming transmission of such STDs as chlamydia and gonorrhea is important, as infertility can result from nontreatment.

epidemiologist at the Centers for Disease Control and Prevention (CDC). Such asymptomatic infections can lead to infertility and ectopic pregnancy, notes Peterman, lead author of the new research.

Among women infected with a sexually transmitted infection at baseline, 19.6% had a new infection at three months, and reinfection at three months was almost as common in men (16.1%), Peterman reports. While risk of reinfection was greatest at the three-month interval, it remained high at six, nine, and 12 months as well, he says. Two-thirds (66.2%) of these sexually transmitted infections were asymptomatic.

The data suggest that patients — men and women — diagnosed with chlamydia, gonorrhea, and trichomoniasis should be advised to return in three months for rescreening because they are at high risk for a new asymptomatic infection, states Peterman. **(To read more about repeat infection, see "Repeat chlamydia infection: Improve partner notification and treatment," October 2006 *STD Quarterly,* p. 1, inserted in the same issue of *Contraceptive Technology Update.)***

"Chlamydia and gonorrhea remain a major threat to reproductive health in the United States," Peterman says. An estimated 2.8 million cases of chlamydia, and more than 700,000 cases of gonorrhea, occur annually in the United States, but many have no symptoms and go undiagnosed, he says. "Both can lead to infertility if left untreated," Peterman says.

The CDC is looking at different strategies to increase return rates for STD testing, but it has not been easy to get people to come back, he notes.

In one recent CDC study, researchers looked at interventions designed to encourage public STD clinic patients infected with chlamydia/gonorrhea to return for rescreening three months after initial treatment.[2] Cost data were collected and combined with study data on return rates and positivity rates among returning patients to compare the interventions' cost-effectiveness.

Patients were randomized to one of three intervention arms:

- In Intervention 1, patients were given a verbal recommendation to return for a chlamydia and gonorrhea screening in three months and given a reminder card with five to seven reasons for returning.
- In Intervention 2, patients were given a brief verbal recommendation and reminder card, but they also were told they would receive $20 on their return as a form of incentive.
- In Intervention 3, patients received a verbal recommendation to return and a reminder card, but they also participated in an interview and counseling session to help them assess risks, identify barriers to returning, and identify reasons and motivations for returning. Patients in the third intervention also were given a reminder phone call and mailed a letter three months after the counseling session to encourage their return.

Data indicate that the brief recommendation with a telephone reminder yielded the highest return rate (33%) and was the least costly in terms of cost per infection treated.[2] In-depth motivational counseling that helped clients identify risk factors and provided reasons for returning was more costly than a phone reminder alone and was not more effective, researchers found.[2]

The CDC is working in Washington, DC, New York City, and San Diego to implement rescreening in STD clinics, reports Peterman. People who return for rescreening at these clinics can choose to have a visit that includes only testing — with no exam — so the visit remains brief, states Peterman.

The clinics are mailing reminders to patients to encourage them to return, reports Peterman. Use of telephone call reminders is being considered; however, the clinics are somewhat limited in what they can do in this area due to concerns for confidentiality and limited staff time, he adds.

"I think we need to get to a point where patients understand that an infection means they need to do some things differently in the future, Peterman says. One of those changes is to be rechecked to see if they have a new infection, he explains, "because they are at risk, and infections are often asymptomatic, they won't know about it without a test. It takes a while for behaviors to change, so as clinicians get in the habit of telling patients to return, and then reminding them, their patients will be more likely to return."

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