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IN THIS ISSUE

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FDA revises Evra safety labeling due to increased estrogen levels

Patch may expose users to about 60% more estrogen than 35 mcg pill

Get ready to discuss questions about the safety of the Evra contraceptive patch (Ortho-McNeil Pharmaceutical, Raritan, NJ) now that the Food and Drug Administration (FDA) has revised the transdermal contraceptive's labeling. The labeling change includes an addition to the drug's warning section to note that the patch exposes women to higher levels of estrogen than most birth control pills. Your patients now will be reading the new bolded warning:

"Hormones from patches applied to the skin get into the blood stream and are removed from the body differently than hormones from birth control pills taken by mouth. You will be exposed to about 60% more estrogen if you use Ortho Evra than if you use a typical birth control pill containing 35 mcg estrogen. In general, increased estrogen exposure may increase the risk of side effects. However, it is not known if there are differences in the risk of serious side effects based on the differences between Ortho Evra and a birth control pill containing 35 mcg estrogen. Talk to your health care provider about how this information relates to your use of Ortho Evra."[1]

The pharmacokinetic profile for the patch differs from that of oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Since the level of estrogen fluctuates greatly in the course of the 24 hours after a birth control pill is taken, the peak level of estrogen actually is higher in women using pills than it is in women using the patch. Peak concentrations for ethinyl estradiol are approximately 25% lower in women using the patch. It is the area under the

curve (AUC) that is 60% higher in patch users.

According to the FDA, the label revision comes as a result of an analysis of the drug, performed by the agency and the manufacturer, which directly compares the estrogen and progestin levels of patch users with those in a typical birth control pill. The agency continues to monitor safety reports for the Ortho Evra patch, while the company is conducting additional studies to compare the risk of developing serious blood clots in women using the patch vs. those using a typical 35 mcg pill.

Ortho-McNeil is issuing a "Dear Health Care Provider" letter to advise clinicians on the labeling change, reports **Julie Keenan**, a company spokeswoman. Information also may be retrieved from the product's web site, www.orthoevra.com, or by calling the Ortho call center at (800) 682-6532, she states.

Is the method safe?

Ortho Evra has been used by more than 5 million women since it received FDA approval in November 2001, and it was studied in 3,300 women prior to its launch. It has gained wide acceptance since its market debut; almost 93% of *Contraceptive Technology Update*'s 2005 Contraception Survey participants said their facility is offering the transdermal contraceptive.

The contraceptive patch has not been recalled. It remains a safe and effective product when used according to the product's label, the company maintains. Its prescribing cautions remain in place: Some women should not use the patch, including women who have blood clots, certain cancers, a history of heart attack or stroke, as well as those who are or may be pregnant, the company advises.

Clinicians already have been fielding questions about the patch's safety after media reports were issued following the April 2004 death of an 18-year-old woman who had been using the transdermal contraceptive and a resulting July 2005 Associated Press (AP) analysis of adverse events reports filed with the FDA surrounding the patch. The AP analysis said 17 patch users had suffered fatal heart attacks, blood clots, and possible strokes since August 2002.

According to **Robert Hatcher**, MD, MPH,

EXECUTIVE SUMMARY

The Food and Drug Administration has revised the labeling for the Ortho Evra transdermal contraceptive including an addition to the drug's warning section to note that the patch exposes women to higher levels of estrogen than most birth control pills.

- The bolded warning specifically states that women who use Ortho Evra are exposed to about 60% more estrogen than if they were taking a typical birth control pill containing 35 mcg estrogen.

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Editorial Questions

Questions or comments?
Call **Joy Daughtery Dickinson** (229) 551-9195.

professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta and chairman of the *CTU* Editorial Advisory Board, the 17 deaths reported by the AP tells nothing of the relative risks of serious complications or deaths in patch users compared to women on combined pills. Numerator data are incomplete, and denominator data are nonexistent; what is needed is a careful epidemiologic analysis of deep vein thrombosis, strokes, heart attacks, and deaths in women on patches and pills, says Hatcher.

"We have no evidence today to say whether very serious complications are more likely in patch users than pill users," says Hatcher. "The fact that estrogen levels in patch users is roughly comparable to levels in women using 50 mcg pills — which are almost never used as a routine contraceptive today — will undoubtedly cause some clinicians to look for a lower estrogen contraceptive than the current patch."

Susan Ballagh, MD, associate professor of obstetrics and gynecology at the Norfolk, VA-based Jones Institute for Reproductive Medicine, believes that despite the new labeling, the patch remains a low-dose combination contraceptive product that can be used by any woman who is a candidate for low-dose combination contraceptives, whether delivered orally, vaginally, or transdermally.

"The new labeling verifies data already apparent that shows that the patch delivers estrogen at the higher rather than lower end of low-dose estrogen alternates," Ballard says. "Women successfully using the patch can continue to use it, as they would any of these effective contraceptive products."

For women experiencing estrogen-related side effects such as breast tenderness or dysmenorrhea from their current combination contraceptive, the patch would not be a first choice, Ballard notes. Those side effects already were known and are described in the labeling, she states.

The new labeling and pharmacokinetic data should not be cause for alarm, observes **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center/Jacksonville. Clinicians may wish to think of the patch in the same category as a 50 mcg combined pill, he notes.

If women are currently using or considering patch use, and view the method as more appropriate for them than alternate birth control methods, then ongoing use makes sense, states Kaunitz. However, if women could confidently use an alternate effective method, such as oral contraceptives, the vaginal ring, an injectable or intrauterine contraceptive, such methods should be reviewed, he notes.

Check pharmacokinetics

A recently published pharmacokinetic comparison of ethinyl estradiol (EE) released from the transdermal patch, an oral contraceptive, and the contraceptive vaginal ring looked at the issue of estrogen exposure.[2] The study evaluated multiple measurements of EE serum levels in women randomly assigned to use the ring, the patch, or a 30 mcg pill.

Although the transdermal patch is designed to deliver a low daily dose of EE, it does not appear to result in low exposure, researchers conclude.[2]

"[A]lthough the transdermal patch delivers only 33% more EE daily than NuvaRing, the exposure to EE in the patch group was approximately 250% greater than in the NuvaRing group," the study's scientists observe.[2]

Women using the ring had a lower fluctuation in serum estrogen levels than with the other methods; women using the Pill had the highest degree of variation in serum concentrations, data indicate. Women who used the patch reported a higher incidence of estrogen-related side effects, including nausea and breast tenderness, than those in the pill and ring groups.[2]

According to the FDA, higher levels of estrogen may put some women at increased risk for getting blood clots. When thinking about prescribing or using Ortho Evra, health care professionals and women need to balance the increased exposure to estrogen against the chance of pregnancy if a birth control pill is not taken daily, the agency advises in a question-and-answer statement.[3]

"Estrogen use is linked to blood clots in the legs and lungs and other clotting problems such as strokes and heart attacks," the FDA advisory states. "It is not known if women using Ortho Evra have a higher risk of serious side effects than women taking the typical 35 mcg estrogen pills."

Women may think that they can decrease the amount of estrogen from the patch by cutting the patch, the FDA advises. Remind them that if the patch is altered or the regimen is not followed as prescribed, the method will not protect against pregnancy.

Remember that the same precautions and danger signals for combined oral contraceptives

apply to the patch. Use the "ACHES" mnemonic (**A**bdominal pain, **C**hest pain, **H**eadaches that are severe, **E**ye problems, and **S**evere leg pain) to teach women the danger signals with patch or Pill use.[4]

Current or potential contraceptive patch users with such risk factors as hypertension, migraines, obesity, or older reproductive age (women in their 40s or early 50s) might particularly be counseled to consider alternate birth control methods, says Kaunitz.

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Continuous regimen OCs: Will U.S. see new pill?

Pill designed with no pill-free intervals

(Editor's note: This article discusses products not yet approved by the Food and Drug Administration.)

Many of your patients may now be using the extended regimen oral contraceptive (OC) Seasonale (Barr Labs, Pomona, NY), where an active pill is taken for 84 days, followed by seven days of placebo pills. But what if there was a pill that would offer continuous dosing with no pill-free intervals?

The Food and Drug Administration (FDA) is reviewing a request from Wyeth Pharmaceuticals of Madison, NJ, for approval of such an OC: Lybrel, a pill with 0.09 mg levonorgestrel and 0.02 mg ethinyl estradiol. If approved, the pill would be the first combination oral contraceptive approved designed to be taken daily, 365 days a year, without a placebo phase.

Research on Lybrel was just presented at the annual meeting of the American Society for Reproductive Medicine (ASRM) in Montreal.[1-4] The efficacy data indicate that the pill was well tolerated and demonstrated the ability to inhibit menses by incrementally inducing amenorrhea (absence of bleeding or spotting) and no bleeding (absence of bleeding, with or without spotting) with increased duration of use. The regimen offers women a safe and effective contraceptive option that reduces the number of bleeding days and symptoms commonly associated with the menses, researchers conclude.[1]

"Overall, the amount of bleeding is small," says **Jeffrey Jensen**, MD, MPH, professor of obstetrics and gynecology at Oregon Health & Science University in Portland and an investigator in the clinical trial. "Women don't become anemic, and hemoglobin actually increases."

Would women be interested in such a pill? In a national survey, 59% of women polled said they would be interested in not menstruating every month, and one-third would choose never to have a period.[5]

Lybrel's efficacy rate appears to be consistent with currently available oral contraceptive products. The efficacy data presented at the ASRM meeting were based on the experiences of 2,134 women who took at least one dose of study drug. Nineteen women became pregnant during use of the regimen. While the Pearl index for the continuous-use regimen will be calculated from pooled results of all phase three studies, the Pearl index for the data presented at the meeting was 1.60 (95% CI, 0.96, 2.49) based on 15,461 pill packs and 13 pill packs per year.[1]

The drug's safety profile appears consistent with currently approved cyclic oral contraceptives. Six

EXECUTIVE SUMMARY

The Food and Drug Administration is reviewing a request from Wyeth Pharmaceuticals for approval of Lybrel, a pill with 0.09 mg levonorgestrel and 0.02 mg ethinyl estradiol. If approved, the pill would be the first combination oral contraceptive approved designed to be taken daily, 365 days a year, without a placebo phase.

- Efficacy data indicate that the pill is well tolerated and demonstrates the ability to inhibit menses by incrementally inducing amenorrhea (absence of bleeding or spotting) and no bleeding (absence of bleeding, with or without spotting) with increased duration of use.
- Research indicates the continuous regimen may be effective for women who suffer pain, mood, or behavioral symptoms linked to their menstrual cycles.

serious adverse events were reported during the study: two cases of cholecystitis, with single appearances of the following conditions: deep vein thrombosis/pulmonary embolism, ectopic pregnancy, prolonged vaginal bleeding, and enlarged uterine fibroids.[1]

Researchers noted a steady increase from baseline in the percentage of participants who reported amenorrhea and no bleeding: 44.8% and 70.8%, respectively, by pill pack seven. Counseling regarding bleeding and spotting is an important part of success with a continuous dosing regimen, says Jensen.

"Although all patients expect to achieve amenorrhea, the experience from every study done with combined OC regimens demonstrate that most women experience a decrease in bleeding days and a substantial increase in spotting days for several months," Jensen observes. "Women who continue with the regimen can expect that their bleeding patterns will improve over time, but it may be six to 12 months before amenorrhea occurs."

At the ASRM meeting, researchers presented data showing that Lybrel significantly alleviates cycle-related symptoms.[4] 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 they continued to report a decrease in symptoms during the two subsequent pill packs.

What advantages can a continuous dosing regimen offer for women who have cycle-related symptoms? Such a regimen may be particularly advantageous for women who suffer pain, mood, or behavioral symptoms linked to their menstrual cycles such as premenstrual syndrome and dysmenorrhea, says **Ellen Freeman**, PhD, professor of obstetrics and gynecology at the University of Pennsylvania in Philadelphia and lead author of the study.

"The continuous regimen appears to significantly reduce these symptoms," she explains. "Other women for various reasons may want to control the timing of their periods or eliminate them entirely."

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Microbicide development gets a corporate boost

(Editor's note: This article discusses products not yet approved by the Food and Drug Administration.)

The long road toward a woman-controlled form of prevention against HIV infection may have just gotten a little shorter with the recent agreement by two major drug companies to license promising compounds at no charge for microbicide development to a nonprofit group.

Bristol-Myers Squibb Co. (BMS) of New York City and Merck & Co. of Whitehouse Station, NJ, have granted the Silver Spring, MD-based International Partnership for Microbicides (IPM) a royalty-free license to develop, manufacture, and distribute specific compounds for use as microbicides in resource-poor countries. The compounds, which are designed to prevent HIV from efficiently entering host cells, are part of a new class of antiretrovirals known as entry inhibitors. The move marks the first time any pharmaceutical company has licensed an anti-HIV compound for development as a microbicide when the class of drugs is so early in development.

The new compounds appear promising. Experiments in female monkeys have for the first time shown that the compounds can protect against an HIV-like virus.[1] The candidates analyzed in the current research were first- or second-generation compounds. Newer, more potent versions are now available and will be the ones most likely to move forward in clinical trials, says **Ronald Veazey**, DVM, PhD, chair of the division of comparative pathology at the Tulane National Primate Research Center in Covington, LA, and lead author of the research paper.

Microbicides may be the best bet in aiding women in the fight against HIV. In 2004, 20 million

EXECUTIVE SUMMARY

Bristol-Myers Squibb Co. and Merck & Co. have granted the International Partnership for Microbicides (IPM) a royalty-free license to develop, manufacture, and distribute specific entry inhibitor antiretroviral compounds for use as microbicides in resource-poor countries.

- Experiments in female monkeys have for the first time shown that the compounds can protect against an HIV-like virus.
- Microbicides may be the best bet in aiding women in the fight against HIV. In 2004, 20 million women were living with HIV.

women around the world were living with HIV, and the upward climb of infections continues, say public health officials.[2] If the spread of disease is left unchecked, women soon will make up the majority of the global total of people infected with HIV, they add.[2]

The new study, funded largely by the National Institute of Allergy and Infectious Diseases, represents the first successful testing of combination microbicides in a primate model. To conduct the research, scientists worked with simian-human immunodeficiency virus (SHIV), a hybrid virus developed from HIV and SIV, which infects only monkeys. Researchers analyzed gels containing two molecules and a peptide in various formulations, all designed to block SHIV from fusing with its target cells at or near the tissue lining of the vagina. Monkeys were given shots of depot medroxyprogesterone acetate (DMPA, Depo-Provera; Pfizer, New York City) to synchronize their menstrual cycles and thin the vaginal membrane to increase their susceptibility to virus infection. Gel was applied vaginally prior to exposing the monkeys to SHIV.

The three inhibitors (BMS-378806 from Bristol-Myers Squibb, CMPD167 from Merck & Co., and C52L, a peptide from Weill Medical College of Cornell University in Ithaca, NY) were effective when used alone and also when tested in combination, research data indicate. Monkeys given the triple combination of microbicides remained virus-free. None of the monkeys experienced vaginal irritation or inflammation from the experimental gels, scientists report.[1] Researchers found that the Merck and BMS compounds could be applied up to six hours prior to exposure to the virus and still offer protection, a finding that could be useful if the compounds make it to real-world application.

The International Partnership for Microbicides now is taking the compounds toward the next step in the development pipeline, says **Zeda Rosenberg**, ScD, chief executive officer of the organization.

Collaboration is an essential part of IPM's strategy in producing potential microbicide candidates. In March 2004, the organization signed an agreement with a Johnson & Johnson subsidiary, Tibotec Pharmaceuticals of Mechelen, Belgium, to develop the subsidiary's TMC120 compound as a microbicide.

For some of the compounds, it could be six months to nine months away from the clinic for Phase I safety testing," notes Rosenberg. "We will only know that once we see how compatible the active drugs are in certain formulations," she adds. "We are getting these drugs as active ingredients, and we need now to formulate them for topical use, either in gels or intravaginal rings."

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Barr set to acquire IUD manufacturer

Intrauterine contraception may see a wider audience in the United States with a major pharmaceutical company's acquisition of the manufacturer of the ParaGard TCu 380A intrauterine device (IUD). Duramed Pharmaceuticals, a subsidiary of Barr Pharmaceuticals in Woodcliff Lake, NJ, has announced its intention to acquire FEI Women's Health of North Tonawanda, NY. At press time, the company said it expected to close the transaction before Dec. 31.

The change comes almost two years after FEI, the longtime manufacturer of the device, secured the U.S. marketing rights for the TCu 380A from the Population Council in New York City. The TCu 380A was codeveloped by the Population Council and FEI in the 1970, and it recently was marketed by Ortho McNeil Pharmaceuticals of Raritan, NJ.

The TCu 380A, approved for contraceptive use up to 10 years by the Food and Drug Administration, is the most widely available IUD in the world.

EXECUTIVE SUMMARY

Duramed Pharmaceuticals, a subsidiary of Barr Pharmaceuticals, has announced its intention to acquire FEI Women's Health, manufacturer of the ParaGard TCu 380A intrauterine device.

- The TCu 380A, approved for contraceptive use up to 10 years by the Food and Drug Administration, is the most widely available intrauterine device in the world.
- U.S. women have two options in intrauterine contraception: the Mirena levonorgestrel intrauterine system marketed by Berlex and the ParaGard.
- The TCu 380A is an effective option for women who choose not to use hormonal contraceptives or who are considering tubal ligation.

In a comparative study of five countries (Italy, Spain, Poland, Germany, and Denmark), the IUD accounted for 9%-24% of all contraceptive use.[1] The proposed change could expand IUD use in the United States, reports **Allan Rosenfield**, MD, dean of the Mailman School of Public Health at the New York City-based Columbia University.

Barr Pharmaceuticals, which plans to market the device through its Duramed subsidiary, says it will bolster its sales force in adding the new contraceptive option to its line of products. "IUDs represent an underutilized contraceptive option for women in the United States, and we believe that we are well positioned to grow this category through consumer and professional education and marketing," says **Bruce Downey**, Barr's chairman and chief executive officer.

U.S. women have two options in intrauterine contraception: the Mirena levonorgestrel intrauterine system marketed by Berlex of Montville, NJ, and the ParaGard TCu 380A IUD. Other IUDs are in use in other global markets, with research ongoing in intrauterine contraception.

Myths still persist

Myths still exist about intrauterine contraception, and misinformation about the method is common, according to information presented at the Association of Reproductive Health Professionals' 2005 meeting.[2]

IUDs are not abortifacients; they do not cause ectopic pregnancies or pelvic infection, according to the presentation given by **Kirtly Parker Jones**, MD, professor in the department of obstetrics and gynecology at the University of Utah Health Sciences Center in Salt Lake City. They also do not decrease the likelihood of future pregnancies. A 2001 case control study helps to refute the myths that IUDs cause pelvic inflammatory infection, increase ectopic pregnancy and infertility, and are inappropriate for young or never-pregnant women.[3]

Intrauterine devices may not need to be removed for treatment of pelvic inflammatory disease[4]; they also do not have to be removed if actinomyces-like organisms are noted on a Pap smear.[2]

The TCu 380A is an effective option for women who choose not to use hormonal contraceptives or who are considering tubal ligation. While the device is approved for 10 years of use in the United States, recent research indicates it may provide effectiveness for a longer period of time.[5]

In a study of women who had been using the device for more than 10 years and who were 35 years of age or older on completion of the 10th year of IUD use, researchers found that found no evidence that the device loses its effectiveness after 10 years of use. "The concept that women who have insertion of a TCu 380A IUD at the age of 25 years or older could use this IUD as a reversible but permanent method of contraception up to the menopause continues to be supported by the accumulation of evidence, although definitive evidence remains to be obtained," the researchers conclude.

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Task force issues new gonorrhea guidelines

When you scan your next chart, it gives the medical history of a 19-year-old woman who has been sexually active with multiple partners and inconsistently uses condoms. She reports a painful

or burning sensation when urinating and increased vaginal discharge. What is your next move?

Be sure to screen for gonorrhea. Infection from the *Neisseria gonorrhoeae* bacterium remains the second most common reportable disease in the United States.[1] The U.S. Preventive Services Task Force (USPSTF) recently issued revised guidelines for routine gonorrhea screening[1], which update earlier 1996 recommendations.[2]

After reviewing evidence, the task force recommends for routine screening high-risk women and against screening low-risk men and women, with insufficient evidence for screening high-risk men. Risk factors for gonorrhea include a history of previous gonorrhea infection, other sexually transmitted infections, new or multiple sexual partners, inconsistent condom use, sex work, and drug use. Risk factors for pregnant women are the same as for nonpregnant women.

Clinicians will need to assess individual risk based on the local epidemiology of disease, say task force members. Local public health statistics can provide guidance to help identify populations who are at increased risk. Communities with a high prevalence of the sexually transmitted disease (STD) may wish to broaden screening, particularly among sexually active young people.[1]

Reports of the STD reached an all-time low in 2004, falling 1.5% between 2003 and 2004, according to 2004 national statistics just issued by the Centers for Disease Control and Prevention (CDC).[3] Despite this reduction, several significant challenges remain, say CDC officials.

Resistance to fluoroquinolone antibiotics, a first-line treatment for gonorrhea, increased from 4.1% in 2003 to 6.8% in 2004, according to CDC's sentinel surveillance in 28 cities. This drug resistance is especially worrisome in men who have sex with men, where it was eight times higher than among heterosexuals: 23.8% vs. 2.9%, says the CDC. In light of such findings, the CDC moved in 2004 to remove its recommendation for use of fluoroquinolones as treatment for gonorrhea among men who have sex with men.

Researchers at Johns Hopkins University have developed a rapid test that can detect potential antimicrobial resistance in the bacteria that cause gonorrhea without culturing the organism. Data on the test, which is not commercially available, were presented at the 2004 Interscience Conference on Antimicrobial Agents, Chemotherapy in Washington, DC.[4]

The test does not require collection, culture, or testing of the bacteria. It uses probe technology to check urine samples or leftover products from other commonly used diagnostic techniques to identify the genes linked to resistance.

The test is only a research assay at this point, says **Charlotte Gaydos**, DrPH, associate professor in the division of infectious diseases at Johns Hopkins University's School of Medicine. "Gonococcal resistance to fluoroquinolones is not a large problem in the U.S. at the moment, except in California," she explains. "Whether this assay would ever be available commercially is doubtful, as it answers a research question for surveillance at the present."

When screening for gonorrhea, clinicians can choose to perform a vaginal culture or use newer screening tests, such as nucleic acid amplification tests and nucleic acid hybridization tests, according to the USPSTF guidelines. Vaginal culture offers accurate screening results when transport conditions are suitable, while newer screening tests have demonstrated improved sensitivity and comparable specificity when compared with cervical culture. Some of the newer tests can be used with urine and vaginal swabs, which enables clinicians to screening when a pelvic examination is not performed.

If gonorrhea is detected, clinicians can choose from one of the following treatments: 400 mg cefixime, 125 mg ceftriaxone, 500 mg ciprofloxacin, 400 mg ofloxacin, or 250 mg levofloxacin. All of these medications can be given in a single dose.[5]

Be vigilant about use of the fluoroquinolones ciprofloxacin, ofloxacin, and levofloxacin; these drugs are not recommended for treatment of gonorrhea infections acquired in Hawaii, California,

EXECUTIVE SUMMARY

The U.S. Preventive Services Task Force has issued revised guidelines for routine gonorrhea screening.

- The task force recommends for routine screening high-risk women and against screening low-risk men and women, with insufficient evidence for screening high-risk men.
- Risk factors for gonorrhea include a history of previous gonorrhea infection, other sexually transmitted infections, new or multiple sexual partners, inconsistent condom use, sex work, and drug use. Risk factors for pregnant women are the same as for nonpregnant women.
- When screening for gonorrhea, clinicians can opt to perform a vaginal culture or use newer screening tests, such as nucleic acid amplification tests and nucleic acid hybridization tests.

Asia, the Pacific, and in other areas with increased prevalence of fluoroquinolone resistance.

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Progestin-only pills: Where do they fit in?

Your next patient is a young mother who just gave birth to a healthy infant eight weeks ago. She is breast-feeding her baby and wants to use a safe method of contraception that will not affect her milk supply. What option will she choose?

If the selected method is the progestin-only pill (POP or mini-pill), your patient falls into a very small segment of contracepting women in the United States. According to the latest review of contraceptive trends, less than 1% of American women select the mini-pill for contraception.[1]

Use of mini-pills may be affected by their effectiveness; according to *A Pocket Guide to Managing Contraception*, about 5% of typical users will experience an accidental pregnancy in the first year, since some women do not take their pills correctly.[2] However, if mini-pills are used consistently and correctly, just three out of 1,000 women will become pregnant.[2]

Prescribing practices for mini-pills call for women to take their pill within a three-hour window each day, which leaves little room for error. Now Cerazette, a new 75 mcg desogestrel mini-pill from Organon NV in Oss, the Netherlands, offers a wider missed window, which may lead to increased use of the progestin-only method.[3]

Unlike other POPs, which draw their effectiveness from thickening cervical mucus so that sperm cannot reach the egg, the desogestrel mini-pill works primarily by preventing ovulation.[2] Based on Cerazette's consistent inhibition of ovulation,[4] European regulators in 2004 extended the drug's missed pill window to 12 hours.[3]

While Cerazette is available in 53 countries, including the United Kingdom, Germany, France, Sweden, and several Latin American countries, it is not available in the United States, says **Corina Ramers-Verhoeven**, an Organon spokeswoman. Mini-pill options available in the United States include Ortho Micronor (0.35 mg norethindrone, Ortho-McNeil Pharmaceuticals, Raritan, NJ), Nor-QD (0.35 mg norethindrone, Watson Pharma, Corona, CA), Ovrette (0.075 mg norgestrel, Wyeth, Philadelphia), Camila (0.35 mg norethindrone, Barr Pharmaceuticals, Pomona, NY) and Errin (0.35 mg norethindrone, Barr Pharmaceuticals, Pomona, NY).

Since mini-pills do not contain estrogen, they represent a good contraceptive choice for breast-feeding women, as well as women with health conditions that preclude use of combined oral contraceptives. Candidates who may initiate POPs include:

- recently postpartum women;
- breast-feeding women;
- smokers older than age 35;
- women with multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension);
- women with an elevated blood pressure;
- women with past history of deep vein thrombosis or a pulmonary embolism;
- women with a known thrombogenic mutation;
- women with coronary artery disease or cerebrovascular disease;
- women with migraine headaches, with or without aura;
- women whose nausea, headaches, depression, or any other symptom has clearly become worse

EXECUTIVE SUMMARY

Prescribing practices for progestin-only pills (POPs or mini-pills) call for women to take their pill within a three-hour window each day, which leaves little room for error. While not available in the United States, Cerazette, a 75 mcg desogestrel mini-pill from Organon NV, offers a wider missed window.

- Unlike other POPs, Cerazette works primarily by preventing ovulation.
- Since mini-pills do not contain estrogen, they represent a good contraceptive choice for breast-feeding women, as well as women with health conditions that preclude use of combined oral contraceptives.

since starting on combined pills, the patch, or the ring;

• women who have or fear chloasma.[2]

Women who use progestin-only pills, including Cerazette, experience irregular bleeding, says **John Guillebaud**, MD, professor emeritus at University College London. The discontinuation rate for Cerazette is very similar to with old-type progestin-only pills, he observes.

Tell women that menstrual irregularity is the most common problem with mini-pills; while the amount of blood lost is less, bleeding may be at irregular intervals and there may be spotting between periods.[2] However, with the absence of estrogen, women may not experience the nausea, headaches, and other symptoms associated with combined oral contraceptives.[2] Mini-pill use may lead to decreased cramps and pain during periods; there also may be decreased pain at the time of ovulation in some women.[2]

For mini-pill users in the United States, clinicians should review what to do if a pill is taken three or more hours late. Counsel women to use a backup method of contraception, such as the condom, until 48 hours after pill-taking resumes.[5]

Take note if women report a history of gestational diabetes; mini-pills may not be the best choice for them. A study that focused on women with a history of gestational diabetes found that those who used progestin-only pills during breastfeeding were almost three times more likely to develop chronic noninsulin-dependent diabetes than women who used nonhormonal methods.[6]

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Raise the antenna on ovarian cancer

The woman sitting in front of you tells you that she has been experiencing abdominal pain, abdominal swelling, gastrointestinal symptoms, and pelvic pain. What is your next move?

According to a new study, four in 10 women with ovarian cancer have symptoms that they tell their providers about at least four months — and as long as one year — before they are diagnosed.[1]

"We found that women with ovarian cancer began to have more abdominal swelling, compared to control women, 10-12 months before diagnosis, and abdominal pain seven to nine months before diagnosis," says lead author **Lloyd Smith**, MD, PhD, professor and chair of the department of obstetrics and gynecology at the University of California Davis Health System in Sacramento.

EXECUTIVE SUMMARY

According to a new study, four in 10 women with ovarian cancer have symptoms that they tell their providers about at least four months — and as long as one year — before they are diagnosed. These symptoms include abdominal pain, abdominal swelling, gastrointestinal symptoms, and pelvic pain.

- Ovarian cancer is the seventh most common cancer in women and ranks fourth as the cause of cancer death in women, according to the American Cancer Society. About 22,220 new cases of ovarian cancer will be diagnosed in 2005; about 16,210 women will die of the disease.
- Birth control pills offer protection against ovarian cancer; ever use of oral contraceptives reduces the risk of ovarian cancer by about 40%.

COMING IN FUTURE MONTHS

- FDA looks at updating condom labeling
- Update: Will United States see over-the-counter EC?
- Syphilis on the rise: What you should do?
- Tackle pelvic inflammatory disease treatment
- Missed pills: How to help patients stay on track

"When diagnostic testing was employed [four to 36 months before diagnosis], most women were sent for abdominal imaging and/or gastrointestinal procedures, and relatively few had pelvic imaging or CA-125 [cancer antigen-125] tests that could lead to a diagnosis of ovarian cancer."

According to the American Cancer Society, ovarian cancer is the seventh most common cancer in women and ranks fourth as the cause of cancer death in women. About 22,220 new cases of ovarian cancer will be diagnosed in 2005; about 16,210 women will die of the disease, according to the organization.[2]

Ovarian cancer often is thought of as a silent killer, coming to the attention of health care providers only at its late stages when prognosis is poor. This new research suggests that ovarian cancer could be diagnosed earlier in some patients.

To perform the study, researchers compared diagnosis codes and claims for diagnostic procedures for 1,985 elderly women with ovarian cancer, 6,024 elderly women with localized breast cancer, and 10,941 age-matched Medicare-enrolled women without cancer.

The investigators found that patients with ovarian cancer were more likely than women in the other two groups to have seen their providers for four particular symptoms: abdominal pain, abdominal swelling, gastrointestinal symptoms, and pelvic pain. Almost half of women with ovarian cancer had physician claims indicating one or more visits for such symptoms four months or more prior to a diagnosis of cancer.

One-quarter of the ovarian cancer patients who reported symptoms four or more months before diagnosis had diagnostic pelvic imaging or CA-125 blood tests. Most of the patients who reported early symptoms received abdominal imaging or diagnostic gastrointestinal studies, tests that are less likely to detect the disease. Within three months of their diagnosis, however, more than half of the ovarian cancer patients received pelvic imaging or CA-125 testing.[1]

"Our recommendation is that women with such symptoms have 'routine' medical evaluation, since ovarian cancer is an uncommon condition and the same symptoms can occur in women without cancer," says Smith. "However, if the symptoms are not explained by such routine medical evaluation, or if they persist, then pelvic imaging and/or CA-125 should be considered."

One line of protection against ovarian cancer may come in the form of the birth control pill. Today's low-dose combined oral contraceptives (OCs) are just as effective as older, high-dose formulations in protecting women from ovarian cancer.[3]

"Ever use of oral contraceptives reduces the risk of ovarian cancer by about 40%," says **Roberta Ness**, MD, MPH, professor of epidemiology, medicine, and obstetrics and gynecology and chair of the department of epidemiology at the University of Pittsburgh. The longer the use, the stronger the effect, she notes. "Protection from oral contraceptives lasts for up to 20 years after stopping the medication."

Progestins may play a role in OCs' protective benefits. Research indicates that OCs with higher levels of progestin are associated with a greater reduction of ovarian cancer risk than those with a lower progestin dose.[4] Findings also indicate that women who took pills with higher progestin levels showed a significant reduction in risk, even when the pills were taken for a short time.

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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 service delivery and the benefits or problems created in patient care in the participant's practice area.
- **Integrate** practical solutions to problems and information into daily practices, according to advice from nationally recognized family planning experts.

1. What does the updated warning state on the labeling for the Ortho Evra contraceptive patch?

A. Women who use Ortho Evra are exposed to about 60% more estrogen than if they were taking a typical birth control pill containing 35 mcg estrogen.
B. Women who use Ortho Evra are exposed to about 25% more estrogen than if they were taking a typical birth control pill containing 35 mcg estrogen.
C. Women who use Ortho Evra are exposed to about 60% more estrogen than if they were taking a typical birth control pill containing 20 mcg estrogen.
D. Women who use Ortho Evra are exposed to about 35% more estrogen than if they were taking a typical birth control pill containing 50 mcg estrogen.

2. What is the name of the levonorgestrel/ethinyl estradiol pill with the continuous dosing regimen under development by Wyeth?

A. Enbrel
B. Lybrel
C. Diane
D. Seasonale

3. The two antiretrovirals licensed to the International Partnership for Microbicides are known as:

A. Sulfated polymers
B. Surfactants
C. Entry inhibitors
D. Acid-buffering gel

4. The ParaGard TCu 380A is approved for how many years' effective use in the United States?

A. Three years
B. Five years
C. Seven years
D. 10 years

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

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™

HPV vaccine on the horizon — Will it be added to immunization schedules?

When you review immunization schedules with your adolescent patients this year, will a vaccine for human papillomavirus (HPV) be added to your discussion list? While no vaccine has yet been approved, recent scientific advances signal that such a vaccine soon may become a reality.

HPVs are the major cause of cervical cancer. HPV-16 causes approximately 50%-60% of cervical cancers, and HPV-18 causes another 10-20%.[1] The American Cancer Society (ACS) estimates about 10,370 cases of invasive cervical cancer will be diagnosed in the United States in 2005, and about 3,710 women will die from the disease.[2]

Just-presented results from a Phase III trial show that an experimental vaccine developed by Merck & Co. in Whitehouse Station, NJ, was completely successful in protecting women against precancerous or noninvasive cervical cancer caused by human papillomavirus (HPV) types 16 and 18.[3]

The Gardasil quadrivalent recombinant vaccine protected all the women who received an initial dose of vaccine followed by a dose at two months and at six months. This cohort, which underwent 17 months of observation, included 5,301 women ages 16-23 who were recruited at 90 research sites in 13 countries.

A total of 5,258 women were inoculated with a placebo vaccine and underwent the same inoculation schedule. Twenty-one were found to have high-grade precancerous cervical lesions or noninvasive cancer.[3]

The presentation follows similar published data from the vaccine's Phase II study, which indicate the quadrivalent HPV vaccine reduced the incidence of HPV infection and any HPV-related diseases by 90% compared with placebo.[4] ***(Contraceptive Technology Update* reported on the research in its article, "Research moves HPV vaccines within view," July 2005, p. 81.)**

GSK Biologicals in Rixensart, Belgium, also has a vaccine, Cervarix, in advanced clinical trials. Research presented in mid-2005 on the bivalent vaccine, which targets strains 16 and 18, indicates it also provides cross-protection against strains 31, 45 and 52.[5]

EXECUTIVE SUMMARY

Recent scientific advances signal that a vaccine for human papillomavirus (HPV) may soon become a reality. New research shows one vaccine was completely successful in protecting women against precancerous or noninvasive cervical cancer caused by human papillomavirus (HPV) types 16 and 18. Companies are now moving toward approval of such vaccines.

- HPVs are the major cause of cervical cancer. The American Cancer Society estimates about 10,370 cases of invasive cervical cancer will be diagnosed in the United States in 2005. About 3,710 women will die from the disease.
- Many public health officials would like to see the HPV vaccine become part of the standard roster of shots that children, especially girls, receive just before puberty.

Merck says it plans to file for FDA approval by the end of 2005, with GSK to soon follow.[6]

How to administer?

Getting a vaccine to market is one step in the prevention wheel. If such a vaccine is approved, how and when will it be administered? Many public health officials would like to see the HPV vaccine become part of the standard roster of shots that children, especially girls, receive just before puberty.[7]

This question was addressed during a recent meeting of the Advisory Committee on Immunization Practices (ACIP), which aids the federal government in designing the most effective means to prevent vaccine-preventable diseases. The panel's guidelines are widely accepted in setting vaccination schedules.

At the meeting, members reviewed results from a survey of American Academy of Pediatricians members, designed to gauge pediatricians' knowledge about HPV disease and their willingness to recommend an HPV vaccine. Pediatricians are willing to administer a vaccine for HPV and are much more likely to vaccinate older female patients (16-18 years vs. 10-12 years), says **Nicole Liddon**, PhD, a medical sociologist in the division of STD prevention at the Centers for Disease Control and Prevention, who presented the material.

The No. 1 barrier to administering a potential vaccine would be the concern that reimbursement would not be adequate, Liddon states. About half of the pediatricians who responded to the survey perceive parental refusal of the vaccine as a potential barrier to vaccination.

"The study also showed that there are gaps in pediatrician knowledge about HPV disease, and that more education on HPV and the HPV vaccine may be needed," states Liddon.

Will shot be accepted?

Human papillomaviruses are a group of more than 100 viruses. More than 30 HPVs are primarily sexually transmitted.[1] Some conservative groups are against making the HPV vaccine mandatory and cite fears that it could send a subtle message condoning sexual activity before marriage.[7]

Since public health officials are looking at administering the shots in young adolescents, how will immunization be received by their parents? Research undertaken by scientists at Indiana University in Indianapolis indicates that parents will be in favor of such a move, says **Gregory Zimet**, PhD, professor of pediatrics and clinical psychology and lead author of the research.[8]

"I think most parents are really interested in protecting their children," he says. "The primary or overriding moral value is protecting their children from disease and from harm."

Will providers want it?

What will be providers' stance on the HPV shot? Based on his research, Zimet contends that they will be interested in such a vaccine. In a survey of members of the American College of Obstetricians and Gynecologists, Zimet found that professional society recommendation is important for acceptability of a potential HPV vaccine.[9]

"If ACIP recommends it and the FDA licenses it, I think the professional organizations will fall into line," Zimet says.

Before any vaccine is introduced, providers will have to be educated on how to talk with patients on the benefits of the vaccine, as well as given specific terminology to ease concerns of patients and parents.[10]

Getting HPV on the radar screens of providers is an important preparatory step, says Zimet. "Cervical cancer is not something that affects children, but prevention is something that has to go into effect during childhood," he notes.

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Raise the radar on chlamydia screening

In reviewing patient files from the last month, how many chlamydia tests were performed at your facility, and how many yielded positive results? If your clinic is seeing an increase in screens, as well as a higher incidence of infection, you are part of a larger nationwide trend.

According to new data released by the Centers for Disease Control and Prevention (CDC), chlamydia was the most common infectious disease in the United States in 2004, with 929,462 cases reported to the CDC.[1] The national rate increased 5.9%, rising from 301.7 cases per 100,000 in 2003 to 319.6 in 2004.

The increase in reported cases may be due to screening and identification rather than an actual increase in infection rates, say CDC officials; however, they caution that most chlamydia cases remain undiagnosed.

At the July 2005 biennial meeting of the International Society for Sexually Transmitted Diseases Research in Amsterdam, the Netherlands, CDC researchers presented data that underscore the heavy burden of chlamydia, particularly in young women. In looking at responses from participants in the National Health and Nutrition Examination Survey from 1999 to 2002, who ranged in age from 14 to 39, scientists found a chlamydia prevalence of 2.2% with no significant differences between women and men overall. Nearly one in 20 women between the ages of 14 and 19 were infected, which is the highest proportion of any age group.[2]

Screening is key

What are some of the steps that CDC is taking to address the burden of chlamydia, especially among women ages 14-19? The CDC and several major medical professional organizations recommend regular chlamydia screening for young sexually active women.

Increased screening efforts are critical to preventing the spread of chlamydia in U.S. youth, says **John Douglas**, MD, director of the Division of STD in the CDC's National Centers for HIV, STD, and TB Prevention. In addition to recommending that all sexually active women younger than 26 receive annual screening, CDC funds programs such as the Infertility Prevention Program, which provides chlamydia screening at public clinics and in nontraditional sites such as detention centers and school-based clinics.

About 40% of women with untreated chlamydia infections develop pelvic inflammatory disease (PID) and 20% of those become infertile, according to the CDC.

"CDC works to increase screening in the private sector by educating physicians about

EXECUTIVE SUMMARY

Chlamydia was the most common infectious disease in the United States in 2004, with 929,462 reported cases. The national rate increased 5.9%, rising from 301.7 cases per 100,000 in 2003 to 319.6 in 2004.

- Increased screening efforts are critical to preventing the spread of chlamydia.
- Interest in chlamydia screening has increased since its 2000 inclusion in the HEDIS (Health Plan Employer Data and Information Set) managed care guidelines.

chlamydia infection rates in their populations and by encouraging health benefit plans to cover chlamydia testing," says Douglas. "CDC also collaborates with professional associations such as the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics to promote increased screening in young people and with the U.S. Preventive Services Task Force to ensure that chlamydia screening guidelines are consistent." ***(Contraceptive Technology Update* reviewed various organization's guidelines in the article, "Group issues guidelines on chlamydia screening," in its *STD Quarterly* supplement, August 2003, p. 3.)**

Add screening to list

Interest in chlamydia screening has increased since its 2000 inclusion in the HEDIS (Health Plan Employer Data and Information Set) managed care guidelines developed by the National Committee for Quality Assurance (NCQA). NCQA is a nationwide organization charged with measuring and reporting on managed care quality. ***(CTU* reported on the HEDIS performance measure in its article, "Women's health issues included in managed care report card," February 2000, p. 17.)**

Such screening pays off. After the obstetrics and gynecology department at Kaiser Permanente of the Mid-Atlantic States introduced a systems-level change in response to the HEDIS measure, the proportion of females who were tested for chlamydia and the number of newly diagnosed females increased.[3]

Kaiser Permanente worked with the CDC to evaluate its chlamydia screening policies, testing practices, and the proportion of 15-year-old to 26-year-old female patients screened in their mid-Atlantic region before and after the measure was implemented.

10% jump in diagnoses

Screening rates increased by almost a third from 1998 to 2001. As a result of increased testing, a 10% increase in the number of new chlamydia diagnoses was recorded.[3]

The proportion of the patient populations testing positive remained at 8% in 1998-1999 and 7% in 2000-2001, which demonstrates the high burden of chlamydia in this commercially insured population.

Despite national recommendations encouraging annual chlamydia screening for young sexually active women, far too many women with chlamydia go undiagnosed every year, says **Gale Burstein**, MD, MPH, the lead CDC researcher on the study.

"A relatively simple systems-level change like the one implemented by Kaiser Permanente's OB/GYN department could help protect the reproductive health of women across the country," Burstein says.

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Register for 2006 STD prevention conference

The 2006 STD Prevention Conference, "Beyond The Hidden Epidemic: Evolution or Revolution?" will be held May 8-11, 2006, at the Hyatt Regency Jacksonville (FL) Riverfront.

The conference will address such issues as vaccines in STD prevention, new strategies for reaching hidden populations, and syphilis elimination. Sponsors of the conference include the Centers for Disease Control and Prevention (CDC), the American Sexually Transmitted Diseases Association, the American Social Health Association, and the National Coalition of STD Directors.

Early-bird registration fee is $185. Early-bird registration deadline is March 13.

To register on-line, go to www.cdc.gov/std conference/default.htm. Click on "registration." ■