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INSIDE

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Improve cervical cancer screening: Review new terminology, guidelines

Use information for better reporting and treatment of cervical abnormalities

Information in two just-published articles is expected to improve care for women with abnormal Pap test results.[1,2] The two articles, published in the April 24, 2002, issue of the *Journal of the American Medical Association (JAMA*) include the overview of the revised system for reporting the results of Pap tests, known as the 2001 Bethesda System, as well as new national consensus guidelines designed to better evaluate women whose Pap tests suggest they may have abnormal cells that may lead to cervical cancer. *(Both articles may be viewed free of charge at the* JAMA *web site, www.jama.ama-assn.org. Click on "past issues," "April 24, 2002," then the article titles to read the articles on-line.)*

The new reporting system is designed to decrease the number of ambiguous results, so providers will need to recommend follow-up testing for a smaller percentage of women. The guidelines give clinicians options to use new technologies to clarify ambiguous cytology results, including liquid-based cytology and DNA testing for human papillomavirus (HPV).

EXECUTIVE SUMMARY

The April 24, 2002, issue of the *Journal of the American Medical Association* offers an overview of the revised system for reporting Pap test results (2001 Bethesda System) and new national consensus guidelines to better evaluate women whose Pap tests suggest they may have abnormal cells that may lead to cervical cancer.

- The 2001 Bethesda System reflects new technologies. It also includes a new category for atypical cells at higher risk of association with precancer, atypical squamous cells — cannot exclude a high-grade lesion (ASC-H), which should help providers detect and treat precancerous lesions more rapidly.
- New national consensus guidelines recommend evaluation and treatment that can prevent precancerous cervix changes from developing into cancer.

Cervical cancer is the second-leading cause of cancer-related death among women worldwide; in the United States, about 13,000 new cases are reported each year, resulting in 4,100 deaths.[3] Pap tests represent an important tool in cancer screening and detection; some 50 to 60 million U.S. women are screened each year with the method.[3]

The 2001 Bethesda System and the management guidelines represent the best way for women to be reassured that they are receiving management and care based on the best available evidence, says **Diane Solomon**, MD, senior investigator at the Bethesda, MD-based National Cancer Institute. Solomon served as coordinator of the Bethesda System and as an investigator in the Atypical Squamous Cells of Undetermined Significance / Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) Trial, which examined options in managing treatment of women with abnormal Pap tests.

The Bethesda terminology and the management guidelines provide more uniform and evidence-based care of women with abnormal Pap tests, says Solomon.

"That is why it is important for clinicians taking care of women to understand the terminology, as well as how that fits in with the guidelines," she notes. "I think the fact that the terminology and the guidelines have been developed in concert with one another actually provides a more seamless management strategy for clinicians to follow."

It is critical that clinicians understand the changes incorporated in the 2001 Bethesda System so that the clinician and the cytopathologist are speaking the same language, maintains **Michael Policar**, MD, MPH, associate clinical professor of obstetrics, gynecology, and reproductive sciences at the school of medicine at the University of California, San Francisco, and vice president for medical affairs at NorthBay Healthcare System in Fairfield, CA. Policar addressed the changes in his lecture, "New Developments in Cervical Cancer Screening and Abnormal Pap Smear Management: Bethesda III and ALTS Trial," at the 2002 *Contraceptive Technology* conferences.

"One of the main purposes for maintaining the Bethesda System is to improve consistency in both the interpretation and management of cervical cancer screening tests," reflects Policar. "Use of the system has helped to reduce variation in interpretation between cytopathology labs as well as in clinician management, and the 2001 modifications should lead to further improvements."

Until now, there have not been uniform standards defining the best way to manage women with abnormal Pap tests, observes **Thomas Wright Jr.**, MD, lead author of the consensus guidelines and associate professor of pathology at the New York City-based Columbia University College of Physicians and Surgeons. As a result, women with abnormal Pap tests may be managed quite differently depending on whom and where they are seen.

"This can lead to inequities in health care such that poor women receive different care than do women with access to the newest technologies," says Wright. "It can also lead to confusion and anxiety; to overtreatment, placing women at risk for injury, and to undertreatment, placing women at risk for the development of cervical cancer."

New technology included

One important change in the 2001 Bethesda System is its recognition of "liquid-based" collection technology. Two companies manufacture liquid-based cytology test kits: Cytyc Corp. of Boxborough, MA, and TriPath Imaging of Burlington, NC. **(See resource box on p. 75 for contact info. *Contraceptive Technology Update* reviewed information on Cytyc Corp.'s ThinPrep Pap Test in its article, "More effective Pap test now available" in its March 1997 issue, p. 35.)**

Previous versions of the Bethesda System required an evaluation of whether the specimen was considered adequate, but the criteria were based on the conventional smear and did not address the new technology. The 2001 Bethesda System incorporates criteria that are specific to the new cell collection method.

The consensus guidelines offer precise management strategies based on liquid-based cytology. One of the most important recommendations

COMING IN FUTURE MONTHS

- Review the new CDC STD Guidelines
- Preview findings on the four-periods-per year pill
- Tips on managing benign cervical lesions
- New methods — Does cost play a factor?
- Update: Status of vaccine for human papillomavirus

RESOURCES

For information on liquid-based cytology test kits, contact:

- **Cytyc Corp.**, 85 Swanson Road, Boxborough, MA 01719. Telephone: (800) 442-9892 or (978) 263-8000. Fax: (978) 635-1033. E-mail: customer service@cytyc.com. Web: www.thinprep.com.
- **TriPath Imaging**, 780 Plantation Drive, Burlington, NC 27215. Telephone: (800) 426-2176 or (336) 222-9707. Fax: (336) 222-8819. E-mail: info@tripathimaging.com. Web: www.tripathimaging.com.

For information on HPV testing kits, contact:

- **Digene Corp.**, 1201 Clopper Road, Gaithersburg, MD 20878. Telephone: (800) 344-3631 or (301) 944-7000. Fax: (301) 944-7121. E-mail: inforeq @digene.com. Web: www.digene.com.

addresses care of women with the most common type of abnormal Pap test, an inconclusive result referred to as ASC-US or atypical squamous cells of undetermined significance.

Before the guidelines were issued, clinicians would follow women with several repeat Pap tests or with colposcopy. The new guidelines say that while these approaches still may be used, HPV testing is preferred whenever liquid-based Pap tests are used.

If liquid-based cytology is used, the laboratory can test the same sample used for the original Pap test for HPV, eliminating the need for a repeat provider visit. Known as "reflex" testing, this form of testing quickly reassures women who are HPV-negative they are unlikely to have a high-grade lesion and that they simply need regular Pap tests. Women who are HPV-positive are identified and scheduled for further evaluation. Just-published research indicates that reflex HPV DNA testing provides the same or greater life-expectancy benefits and is more cost-effective than other management strategies for women diagnosed as having ASC-US.[4] **(HPV testing kits are manufactured by Digene Corp. of Gaithersburg, MD; see resource box, above. Review HPV DNA test information in the article, "HPV DNA tests: Studies target use for cancer screening," included in the May 2000 *STD Quarterly* inserted in *CTU.)***

The approach of using reflex HPV DNA testing allows 50% of women with ASC-US who are found to be HPV DNA negative to return for annual cytological screening without having to return for additional testing, says Wright.

More than 60% of all Pap tests in the United States are liquid-based, and this number is considerably higher in the private sector, says Wright. He predicts an almost complete conversion to liquid-based cytology within the next two years.

New term flags cases

The older Bethesda System grouped all cells considered equivocal — atypical but not clearly precancerous — into the ASCUS category. The 2001 Bethesda System adds a new category for atypical cells at higher risk of association with precancer: atypical squamous cells — cannot exclude a high-grade lesion (ASC-H). By highlighting such cases, the new system should help providers detect and treat precancerous lesions more rapidly. In addition, the term "atypical squamous cells favor reactive" has been eliminated to focus attention on women at higher risk of having an abnormality.

The ASC-H category is useful because it highlights a group of women who are at increased risk for underlying high-grade lesions, says Solomon. The need for such a category was demonstrated in the findings of the ALTS trial, she notes.[5]

"The addition of the ASC-H category hopefully will simplify the management of women with ASC smears, in addition to prompting colposcopy referral for women with ASC findings who are most likely to have high-grade SIL [squamous intraepithelial lesion]," says Policar.

The 2001 Bethesda System also includes changes in how specimens are categorized. The new terminology uses three streamlined categories — "negative," "epithelial cell abnormality," and "other" — to depict whether a result is negative or positive. Whenever a report indicates either "epithelial cell abnormality" or "other," it will offer additional interpretations and diagnoses.

While the new terminology and management guidelines represent important strides in medical care, the emphasis should remain on screening women for cervical cancer, says Solomon.

"We focus on new technologies in screening and management of the abnormal Pap test, but what we can never forget is that in order to have the greatest impact on decreasing mortality from cervical cancer, we need to screen women who aren't currently being screened," she notes. "[Providers who work in clinic settings] need to be given a pat on the back and an extra note of congratulations because they are really on the forefront of trying to reduce

cervical cancer mortality by screening women who may otherwise fall through the cracks."

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Collaboration was key to terminology, guidelines

The 2001 Bethesda System is the product of an April 30-May 2, 2001, workshop sponsored by the Bethesda, MD-based National Cancer Institute and numerous professional societies. In addition to the input received by the more than 400 workshop participants, even broader participation in the revision process was made possible through a dedicated web site (www.bethesda2001.cancer.gov). More than 1,000 individual comments were received on the draft recommendations.

Representatives from 29 medical organizations and professional societies involved in women's health care reviewed evidence from a broad range of studies to develop the Consensus Guidelines. The development of the guidelines was led by the Hagerstown, MD-based American Society of Colposcopy and Cervical Pathology, which sponsored a consensus workshop Sept. 6-9, 2001, in Bethesda. *(Check the Society's web page for information on the guidelines at www.asccp.org.)*

The new terminology and guidelines are the result of a further "fine-tuning" of the Bethesda System, says **Michael Policar**, MD, MPH, associate clinical professor of obstetrics, gynecology, and reproductive sciences at the School of Medicine in the University of California, San Francisco, and vice president for medical affairs at NorthBay Healthcare System in Fairfield, CA. He sees the most recent changes as "evolutionary, not revolutionary."

"The main difference over time is that the classification system and guidelines are becoming more evidence-based; many of the modifications in the 2001 Bethesda System are consequent to the findings in the ALTS [Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study] Trial,"[1-4] he notes.

The 2001 Bethesda System's terminology does eliminate some confusing terms and definitions and clarifies findings that require further evaluation, all which should help providers make decisions about appropriate follow-up care. But while the new format may make lab results easier to interpret, providers will need to carefully read the comments section to learn about cellular characteristics, say medical experts.

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Abortion pill advisory issued

Danco Laboratories LLC of New York City, manufacturer of Mifeprex (mifepristone), has issued a letter to providers that alerts them that six women have developed serious illnesses and two have died after taking the abortion drug.[1] No causal relationship has been established between the drug and the illnesses in any of the cases, the letter states.[2]

EXECUTIVE SUMMARY

The manufacturer of the abortion drug mifepristone and the Food and Drug Administration (FDA) have issued a letter to providers alerting them to the recent deaths of two patients who took mifepristone.

- No causal relationship has been established between the drug and the illnesses in any of the cases.
- In all of the reported cases, misoprostol, the second drug administered in the abortion drug regimen, was given vaginally, not orally, which is the approved method. The FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

Officials with Danco, the Population Council (the New York City-based research organization that granted exclusive license to Danco to manufacture, market, and distribute Mifeprex) and the Food and Drug Administration (FDA) said it was important to provide prescribers of Mifeprex with updated safety information, remind them of their responsibility to provide patient counseling, and to report certain events to Danco, states **Heather O'Neill**, Danco spokeswoman.

The letter reminds providers that the FDA-approved regimen for administration of Mifeprex is:

• 600-mg Mifeprex taken orally in the office or clinic;

• 400 mcg of misoprostol taken orally in the office or clinic 48 hours after the Mifeprex.

In all of the reported cases, misoprostol was given vaginally, not orally, which is the approved regimen, the letter states. In information posted by the FDA, the agency states that it has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.[3] (*Read the provider letter, as well as answers to frequently asked questions, at the FDA Medwatch web site, www.fda.gov/medwatch. Click on "2002" under "Safety Alerts for Drugs," then click on "Drugs." Click on "Mifeprex" to read the two items.)*

The move to issue the advisory letter came after Danco Laboratories received three reports of ruptured ectopic pregnancies, including one death from hemorrhage due to a ruptured ectopic pregnancy.[1] In addition, the company has recorded two cases of serious systemic bacterial infection, one of them fatal, following treatment with Mifeprex and misoprostol, as well as a report of myocardial infarction occurring in a 21-year-old woman three days following the mifepristone/misoprostol regimen.

Providers are reminded that confirmed or suspected ectopic pregnancy is a contraindication for the use of mifepristone and should be ruled out prior to initiating drug treatment. **(Review "Gauging the Effectiveness of Mifepristone and Misoprostol," the February 2001 *Contraceptive Technology Reports* inserted in the February issue of *Contraceptive Technology Update.)***

"Because ectopic pregnancy may be present despite your best efforts to rule it out before starting Mifeprex treatment, you should be mindful of the possibility of an ectopic pregnancy throughout the treatment period and have a plan for its management," the letter states.

In the case of the infection reports, the company notes that while serious infection in medical abortion is rare, providers should be aware of such possibilities if patients report symptoms or have signs of infection. Women should be reminded to contact providers immediately if they have severe pain, heavy bleeding, bad-smelling discharge, or fever.

During the first office visit for medical abortion, women should be presented the Mifeprex medication guide, and they also should read and sign the patient agreement provided by the company. In addition, providers are reminded to report serious adverse events including death, hospitalization, blood transfusion, and other major events to the company, as well as cases of ongoing pregnancy following treatment with the Mifeprex regimen.

Affirm abortion safety

Clinicians should convey to women the safety of medical abortion through talking not only about their own personal experiences in providing medical abortion, but also pointing to the extensive literature surrounding medical abortion, says **Vanessa Cullins**, MD, vice president for medical affairs for the New York City-based Planned Parenthood Federation of America.

"There are over half a million women that have had safely had medical abortion performed worldwide, and in the United States, and we are gathering extensive data that indicate that medical abortion is provided very safely, whether using the FDA-approved protocol or the evidence-based alternative, which uses lower doses of mifepristone," she states. **(See "Slow entry seen for mifepristone in 2001," in *CTU,* December 2001, p. 140.)**

According to Cullins, Planned Parenthood

affiliates have performed about 13,000 medical abortions using mifepristone since its U.S. introduction and have experienced very few adverse effects.

"Less than 1% of women have had adverse events, and no one has died from medical abortion in our experience," she reports. "And in fact, our complication rates are lower than those seen in the literature."

Planned Parenthood's medical protocol for the administration of mifepristone is designed to confirm the presence of an intrauterine pregnancy, rule out the possibility of an ectopic pregnancy, and ensure continuing patient support, states Cullins in a letter to the editor following the issuance of the Danco Laboratories letter.[4] Patients receive comprehensive counseling, including information about when and how to seek additional information and care, should the need arise, she notes.

When the manufacturer's letter was issued, Cullins says Planned Parenthood forwarded information to its affiliate medical directors, and they in turn advised their staff to provide reassurance if they received any type of inquiries from women.

"Both providers and women should have confidence in medical abortion," says Cullins.

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Reinforce instructions after Micronor alert

EXECUTIVE SUMMARY

The manufacturer of the progestin-only birth control pill, Ortho Micronor (norethindrone), has issued an alert that certain lots of the drug contain incorrect information in the patient leaflet that, if followed, could compromise the drug's efficacy.

- The information is contained in the Detailed Patient Labeling accompanying the pills. The section under the heading "Instructions for Using Your DIALPAK Tablet Dispenser" incorrectly states "If you miss any of pills 22 through 28, you will still be protected."
- The company emphasizes that women taking Ortho Micronor, or any progestin-only birth control pill, should take one pill every day without any breaks for maximum effectiveness.

Check your inventory of Ortho Micronor progestin-only pills. While there are no problems with the pills themselves, certain lots of the drug contain incorrect information in the patient leaflet that, if followed, could compromise the drug's efficacy.

According to the pill manufacturer, Ortho-McNeil Pharmaceutical of Raritan, NJ, certain lots of the drug contain incorrect information in the patient leaflet, which Ortho-McNeil refers to as the Detailed Patient Labeling. The following incorrect statement is found under the heading "Instructions for Using Your DIALPAK Tablet Dispenser":

"If you miss any of pills 22 through 28, you will still be protected."

The company issued an advisory on April 4, 2002, citing the following Ortho Micronor product lot numbers:

- 11M001;
- 11M002;
- 11M019;
- 12A029;
- 12C003;
- 12C004;
- 12C030.

About 500,000 cycles of the drug were involved in the alert, says **Kellie McLaughlin**, director of global pharmaceutical communications for New Brunswick, NJ-based Johnson & Johnson, Ortho-McNeil's parent company. The lot numbers were shipped starting Jan. 30, 2002. New shipments have been suspended until new patient leaflets can be printed, packaged, and shipped with the product. The advisory only addresses Ortho Micronor pills; none of the other eight birth control pills marketed by Ortho-McNeil are included in the alert.

Health care providers and pharmacists have been asked to check product lot numbers, remove the incorrect patient leaflet, and insert the correct leaflet when dispensing the product, says McLaughlin. Direct purchasing chains and

wholesale distributors have been asked to return the product lots in question, she states. (The corrected patient leaflet, as well as a health care professional letter, frequently-asked question sheet, and press release, are available at www.ortho micronor.com. *Click on "Important Alert About Ortho Micronor," then click on the links for each item.*) Providers who have further questions may contact the company's customer communications center at (800) 632-7497.

According to the company, women taking Ortho Micronor, or any progestin-only birth control pill, should take one pill every day without any breaks for maximum effectiveness.[1] Women who miss one pill should take the missed pill as soon as possible and continue taking a pill each day at the regular time, the company advises. A backup method of birth control (such as a condom or spermicide) must be used for the next 48 hours. Women who miss more than one pill should use a backup method of birth control and contact a health care professional immediately, states the company. (*According to* A Pocket Guide to Managing Contraception, *if a woman misses a pill by more than three hours from her regular time, she should take the missed pill(s) and use backup contraception for seven days. She should consider using emergency contraception if intercourse occurred in the past three to five days.)*[2]

Same time, every day

Although not widely used in the United States, progestin-only pills offer an important contraceptive option since they may be used by women who desire immediately reversible hormonal protection but who have contraindications to the estrogen in combined pills. Unlike combined oral contraceptives, progestin-only pills are taken continuously, with no hormone-free intervals between cycles. **(For a review of progestin-only pills, see "Maximizing the use of the progestin minipill," *Contraceptive Technology Update,* February 1999, p. 19.)**

Three progestin-only pills are available in the United States: Ortho Micronor, Nor-QD (Watson Laboratories, Corona, CA), and Ovrette (Wyeth-Ayerst Laboratories, Philadelphia.) Ortho Micronor contains 0.35 mg of the progestin norethindrone, as does Nor-QD; Ovrette contains 0.075 mg of norgestrel.

Among typical couples who use progestin-only pills, about 5% will experience an accidental pregnancy in the first year.[2] However, if the pills are used consistently and correctly, just one in 200 women will become pregnant.[2]

Progestin-only OCs, often referred to as minipills, are formulated at a very low dose, so low in fact that ovulation often occurs in those using this method of contraception, says **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center / Jacksonville. If users are not "religious" in consistently taking tablets at the same time each day, the anti-fertility impact of the minipills (including cervical mucus changes) may diminish, permitting fertilization, he states.

In the United States, the great majority of minipill users are nursing mothers, Kaunitz observes. Progestin-only pills represent a good contraception option for such women, since they have no adverse effects on lactation. Most research has found either that they have positive effects — increasing milk quantity or improving its nutritional quality — or that they have no effect.[3] Women who choose progestin-only pills can use them and continue to breast-feed until lactation cessation.[3]

Because lactating women are intrinsically subfertile, precautions regarding taking minipills at the same time each day may not be critical, Kaunitz notes. However, highly fertile women relying on minipills for contraception, as well as their clinicians, should pay close attention to well-timed consistent daily pill-taking, he states.

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NuvaRing announces free voucher program

Will women in your care be interested in using the contraceptive vaginal ring (NuvaRing, Organon, West Orange, NJ) when it becomes available in summer 2002? Their interest may be piqued by the manufacturer's recent announcement to

EXECUTIVE SUMMARY

When the NuvaRing contraceptive vaginal ring enters the U.S. market this summer, its manufacturer will introduce a voucher program for one free ring per patient.

- When the product is launched, women can sign up for the vouchers at www.nuvaring.com. Providers also will be given voucher forms to give out with NuvaRing prescriptions.
- The device is a small, flexible, transparent ring that releases a continuous low dose of estrogen and progestin over 21 days.
- The cost is expected to be comparable to combined oral contraceptives.

issue vouchers for one free ring per patient.

How long will the voucher program be in effect? At this point, there is no cut off date, says **Amanda Mason**, Organon spokeswoman.

"Organon intends to continue with this program as long as women are taking advantage of it," states Mason. "There is no limit to the number of women who can receive a free NuvaRing, but each woman is limited to one free trial within the one-year expiration date on the voucher."

The contraceptive vaginal ring is expected to hit U.S. drugstore shelves this summer. It received Food and Drug Administration approval in October 2001. Cost for the device is expected to be comparable to monthly supplies of combined oral contraceptives. ***(Contraceptive Technology Update* reported on the approval; see "Organon launches NuvaRing, first combined contraceptive vaginal ring," December 2001, p. 137.)**

When the product is launched, women can sign up for the vouchers at its web site, www.nuvaring.com. Providers also will be given voucher forms to give out with NuvaRing prescriptions; Organon sales representatives will distribute the forms with product starter kits, says Mason.

While vaginal rings have been used for hormone replacement therapy, NuvaRing represents the first contraceptive vaginal ring. The device is a small, flexible, transparent ring; it works by releasing a continuous low dose of estrogen and progestin (an average 0.120 mg of etonogestrel and 0.015 mg of ethinyl estradiol) per day over a 21-day period of use. It is inserted in the vagina, where it remains for three weeks, and then is removed for one week. **(Get in-depth information on the NuvaRing; read the *Contraceptive Technology Reports* "The Vaginal Contraceptive Ring — Efficacy, Caution, and Instructions" inserted in the February 2002 issue of *CTU.)***

In a one-year, multicenter study assessing the contraceptive efficacy, cycle control, tolerability, and acceptability of the contraceptive, 1,145 women were exposed to the vaginal ring for 12,109 cycles (928 woman-years). Six pregnancies occurred during treatment, giving a Pearl Index of 0.65 (95% confidence interval 0.24 — 1.41)[1] Cycle control was very good, because irregular bleeding was rare, reported investigators.

The exact positioning of NuvaRing within the vagina is not critical for it to work; because the device is not a barrier contraceptive, it cannot be incorrectly inserted within the vagina. Women can insert the device lying down, squatting, or standing with one leg up.

When counseling women on NuvaRing use, remember to inform them that device use does not prevent HIV infection or sexually transmitted diseases.

Check provider program

Some providers are getting a head start on introducing the NuvaRing through a "premier program" instituted by Organon. Some 6,500 physicians and nurse practitioners signed up for the program; each could enroll up to five patients, offering six months' free supplies of rings. Enrollment in the program is now closed.

According to the company, preliminary findings indicate that 89% of patients enrolled in the program were satisfied with NuvaRing compared to their former method of contraception, and 94% are likely to continue using the device. Additional information from the program will be reported later this year.

The convenience of the device is a major advantage for patients seen by **Raquel Arias**, MD, associate professor of clinical obstetrics and gynecology and associate dean for women in the Keck School of Medicine at the University of Southern California in Los Angeles. Arias, who also served as an investigator in the U.S. trial of the NuvaRing, says the "one-size-fits-all" device makes it easy for women to insert the NuvaRing. Since placement is not key to its efficacy, it makes instruction for use that much easier, she notes.

Arias says her patients report no problems in wearing the device, and they say their partners cannot tell when the device is in place. She has recorded no patient problems with breakthrough bleeding or spotting.

"It is a good method for people who want to have effective contraception that is more convenient than a daily method, and is just as effective, if not more effective," observes Arias. "If efficacy and convenience are important, then I think this is a great option for women who would otherwise be good candidates for birth control pills."

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Does weight play a role in effectiveness?

As the contraceptive transdermal system (Ortho Evra, manufactured by Ortho-McNeil Pharmaceutical of Raritan, NJ) moves into wide availability in the United States this summer, providers can expect plenty of questions from women interested in the new method. What will you tell your heavier patients about the contraceptive efficacy of the patch?

An analysis of pooled data from three pivotal studies show that in contraceptive patch users, the overall annual probability of pregnancy was 0.8% and the method failure probability was 0.6%.[1] While contraceptive failure was low and uniformly distributed across the range of body weights in women lighter than 198 pounds, in women at or more than that weight, contraceptive failures may be increased, researchers conclude.

Body weight equal to or more than 198 pounds is the first item listed under "Precautions" in the Ortho Evra labeling, notes **Kellie McLaughlin**, director of global pharmaceutical communications for New Brunswick, NJ-based Johnson & Johnson, Ortho-McNeil's parent company. The labeling states: "Results of clinical trials suggest that Ortho Evra may be less effective in women with body weight $\geq$198 lbs. (90 kg) than in women with lower body weights."

When it comes to efficacy and the contraceptive patch, there are a number of theories as to why weight may play a factor:[2]

- Women with more subcutaneous fat may have poorer absorption since the distribution of hormones into the serum is dependent on transdermal absorption.
- Absorption of hormones in larger women may vary between sites.
- Steady-state levels may take longer to reach in heavier women, reducing efficacy during the initial week of the cycle.
- Clearance of norelgestromin and ethinyl estradiol may be increased in larger women, by renal clearance or total body clearance.
- Larger women may have lower circulating levels of the hormones contained in contraceptive methods because of dilution in a larger total blood volume.
- Ovulation rates and cervical mucus effects may be differentially affected by confounding factors in obese women.

While more research may be indicated on patch efficacy and weight, the company does not plan to pursue further studies at this time, says McLaughlin.

What about the Pill?

Consideration of a woman's weight may be an important element when it comes to prescribing oral contraceptives (OCs), suggest results from a just-published study.[3] Investigators conducted a retrospective cohort analysis of data from 755 randomly selected female enrollees of Group Health Cooperative of Puget Sound who completed an in-person interview and dietary questionnaire between 1990 and 1994 as control subjects for a case-control study of ovarian cysts. Among the 618 women who were OC ever-users, scientists used mathematical models to estimate the relative risk of pregnancy while using OCs

EXECUTIVE SUMMARY

Recent data have raised questions about the efficacy of the new contraceptive transdermal system (Ortho Evra, Ortho-McNeil Pharmaceutical, Raritan, NJ) in women with greater baseline body weight. The contraceptive patch is expected to be widely available in the United States in summer 2002.

- While research indicates that contraceptive failure was low and uniformly distributed across the range of body weights in women lighter than 198 pounds, in women at or above that weight, contraceptive failures may increase. The company notes this finding in the "precaution" area of the package labeling.
- Researchers are examining the possible effect of weight on oral contraceptive effectiveness.

associated with body weight quartile.

During 2,822 person-years of OC use, 106 confirmed pregnancies occurred (3.8 per 100 person-years of exposure). After controlling for parity, women in the highest body-weight quartile (70.5 kg or more) had a significantly increased risk of OC failure (RR 1.6, 95% confidence interval [CI] 1.1, 2.4) compared with women of lower weight. Higher elevations of risk associated with the highest-weight quartile were seen among very low-dose OC users (RR 4.5, 95% CI 1.4, 14.4) and low-dose OC users (RR 2.6, 95% CI 1.2, 5.9), controlling for parity, race, religion, and menstrual cycle regularity.

Scientists plan to further examine this issue, reports the paper's lead author, **Victoria Holt**, PhD, MPH, professor in the department of epidemiology at the Seattle-based University of Washington. With funding from the Bethesda, MD-based National Institute of Child Health and Human Development, Holt and collaborating researchers are conducting a case-control study of pregnancies among current OC users. Scientists are obtaining information about women's weight before and during OC use, and they also are obtaining details of their pill-taking habits and concurrent illnesses and medications that might influence OC effectiveness.

Holt says her published paper does not indicate that it is advisable to just prescribe a higher-dose pill for heavy women, as side effects of higher-dose pills may be greater, especially for overweight women.

If the findings of the initial paper are confirmed through further studies, providers may want to discuss other contraceptive options with heavy women who have a strong desire to avoid unintended pregnancy, says Holt. These women may wish to consider use of a second type of contraception along with OCs, or choose another form of birth control, she suggests.

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FDA gives nod to label change for misoprostol

The drug label for misoprostol (Cytotec, Pharmacia Corp., Peapack, NJ) has been revised to reflect its use in labor induction, as well as its role in the Food and Drug Administration (FDA)-approved regimen for medical abortion.

The original labeling for the drug stated that pregnant women should never use it. The new labeling clarifies that the contraindication is for pregnant women who are using misoprostol to reduce the risk of nonsteroidal anti-inflammatory drug-induced stomach ulcers. The contraindication now refers to the drug's approved indication; it does not contraindicate off-label uses.

Pharmacia received notification of the FDA approval of the new wording in April 2002, confirms **Mark Wolfe**, director of corporate communications. The company had worked with the federal agency for more than two years to revise the drug labeling, according to a statement issued by Pharmacia.[1]

"We recognize that physicians will use their own professional judgment to prescribe any pharmaceutical product outside its FDA-approved indication in the interest of their patients based on published research, expert clinical opinion, and their experience," reads the statement. "As Pharmacia has consistently stated, we intend to continue making Cytotec available to physicians and patients."

The FDA approved misoprostol in 1988 for the prevention of gastric ulcers associated with the use of NSAIDS. Since that time, however, the drug has been used on an off-label basis, particularly for cervical ripening as a prelude to induction of labor

EXECUTIVE SUMMARY

The label for the drug misoprostol (Cytotec, Pharmacia Corp., Peapack, NJ) has been changed to reflect the fact that it is widely used by providers to induce labor and also is part of the Food and Drug Administration (FDA)-approved regimen for medical abortion.

- The label for the drug had stated that pregnant women should not take the drug under any circumstances, a warning that the FDA has removed.
- The new label will keep the warning that women who are taking the drug for its approved indication to treat ulcers should not become pregnant.

and as the second component to early medical abortions using mifepristone.

Review label changes

The new labeling includes a new labor and delivery section and provides safety information related to those uses. It also provides new information that uterine rupture, an adverse event reported with Cytotec, is associated with risk factors, such as later-trimester pregnancies, higher doses of the drug, including the manufactured 100-mcg tablets, prior cesarean delivery or uterine surgery, and having had five or more previous pregnancies.

According to the FDA, risk factors allow physicians to identify patients who may be at greater risk for these adverse events; the new information may guide safer use of the drug.

Since Pharmacia has not studied the drug for the purpose of labor induction or for the early termination of pregnancy, it contends that it "does not have the necessary relevant information to support its therapeutic use nor to provide guidance in these areas," according to its corporate statement.

The new labeling for Cytotec is an acknowledgment of the use of the drug for cervical ripening in labor induction, notes **Stanley Zinberg**, MD, MS, ACOG's vice president of practice activities and deputy executive vice president.

"It is still ACOG's opinion that based on current evidence, Cytotec is a safe and effective agent for the induction of labor when used appropriately," he states.

Although the new labeling does not approve the use of misoprostol in pregnancy, it recognizes that the drug is used for abortion and obstetrical practice and that a large body of evidence supports these uses, says **Philip Darney**, MD, MSc, professor at the University of California, San Francisco, and chief of the department of OB/GYN at San Francisco General Hospital Medical Center. The change ought to make clinicians, as well as their hospitals or other employers, feel more confidant about evidence-based applications of misoprostol for the care of pregnant women, Darney asserts. (The new labeling is available in Adobe Acrobat PDF format at the FDA web site www.fda.gov/medwatch; click on "Safety Information," then "2002" under "Safety Alerts for Drugs, Biologics, Devices, and Dietary Supplements." Click on "Drugs" to find the PDF document for Cytotec.)

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CE/CME Questions

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

- Name the category in the 2001 Bethesda System for atypical cells at higher risk of association with precancer.
- Cite the federal Food and Drug Administration (FDA)-approved regimen for use of Mifeprex in medical abortion.
- Give the reason why Ortho-McNeil Pharmaceutical issued a 2002 alert on certain lots of Micronor progestin-only pills.
- State the weight level noted in the "precaution" area of the Ortho Evra transdermal system.

25. What is the category in the 2001 Bethesda System for atypical cells at higher risk of association with precancer?

A. ASC-H
B. ASC-US
C. AGC
D. AIS

26. What is the FDA-approved regimen for use of Mifeprex in medical abortion?

A. 600-mg Mifeprex taken orally in the office or clinic; 400 mcg of misoprostol inserted in the vagina in the office or clinic 48 hours after the Mifeprex.
B. 400-mg Mifeprex taken orally in the office or clinic; 400 mcg of misoprostol taken orally in the office or clinic 48 hours after the Mifeprex.
C. 600-mg Mifeprex taken orally in the office or clinic; 400 mcg of misoprostol taken orally in the office or clinic 48 hours after the Mifeprex.
D. 400-mg Mifeprex taken orally in the office or clinic; 600 mcg of misoprostol taken orally in the office or clinic 48 hours after the Mifeprex.

27. Why did Ortho-McNeil Pharmaceutical issue a 2002 alert on certain lots of Micronor progestin-only pills?

A. The pills were unsafe for use.
B. Certain pill packs were missing the correct amount of pills.
C. The company had inadvertently shipped combined oral contraceptives in the Micronor packs.
D. The patient leaflets contained incorrect information that, if followed, could compromise the efficacy of the pills.

28. What weight is stated in the "precaution" area of the Ortho Evra transdermal system as being a potential flag for contraceptive efficacy?

A. Body weight equal to or more than 150 pounds
B. Body weight equal to or more than 198 pounds
C. Body weight equal to or more than 220 pounds
D. Body weight equal to or more than 300 pounds

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