AMERICAN HEALTH CONSULTANTS

CONTRACEPTIVE TECHNOLOGY UPDATE®

A Monthly Newsletter for Health Professionals

INSIDE

OCTOBER 2002

VOL. 23, NO. 10 (pages 109-120)

Don't count implants out: 2 options may take Norplant's place

While suspect Norplants were found safe, implant won't be reintroduced

Rewind to August and September 2000: Two manufacturer's advisories caution that certain lots of Norplant implants may be ineffective and alert clinicians to provide backup contraception for women using the suspect kits. Shipments of the product are suspended while effectiveness testing is conducted.

Fast-forward to July 2002: An announcement informs providers that the suspect lots have been found effective, and there is no need to use backup contraception. However, due to what the manufacturer, Wyeth Pharmaceuticals of Madison, NJ, terms "limitations in product component supplies," the Norplant System will not be reintroduced in the United States. **(See "Check Norplant stock, company says: Recent batches might be ineffective," *Contraceptive Technology Update,* October 2000, p. 117, and "Are Norplant's days numbered in the U.S.? Test results could decide its fate," November 2000, p. 129.)**

Before you cross implants off the contraceptive options list, however, know this: Organon of West Orange, NJ, plans to submit its New Drug Application to the Food and Drug Administration (FDA) for its single-rod implant Implanon in the fourth quarter of 2002, and Wyeth is planning to

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Women can stop using backup contraception in addition to their Norplant implants now that Wyeth Pharmaceuticals has announced that suspect lots have been found effective. However, Wyeth will not reintroduce the six-rod levonorgestrel implant in the United States.

- Organon plans to seek approval for its Implanon single-rod implant in the fourth quarter of 2002. Wyeth plans to make its two-rod levonorgestrel implant available in the United States.
- Wyeth has issued a provider letter and consumer information sheet on the backup contraception advisory. It also offers a toll-free hotline for provider and consumer questions.

make its two-rod levonorgestrel implant available in the United States.

Overcoming the barriers

Properly introduced, the implant technology still has great potential, says **Allan Rosenfield**, MD, dean of the Mailman School of Public Health and DeLamar professor of public health and obstetrics/gynecology at Columbia University in New York City. However, reintroduction of contraceptive implants in the United States will be a difficult task due to the Norplant experience, he notes.

"It certainly has not been easy getting [intrauterine devices] the kind of acceptance and use they deserve, with the Dalkon Shield experience still present so many years later," comments Rosenfield, who led a national committee that examined the U.S. experience with Norplant.

He says the key to successful implant reintroduction will be a careful marketing strategy, first implemented in family planning clinics in both medical school settings and in Planned Parenthood and other public programs, then with private clinicians through the normal channels of continuing education and marketing visits.

"I would focus on the available data on the single- and two-rod implants, the ease of insertion and removal, and the fact that these are new innovations, based on, but different from, the older six-rod Norplant system," suggests Rosenfield. "I would make absolutely certain that clinicians are well trained both to insert properly and to remove the devices."

Thorough training will be crucial, agrees **Paul Blumenthal**, MD, associate professor of obstetrics and gynecology at Johns Hopkins University in Baltimore. Manufacturers will need to create "new identities" for these products when marketing them, he says.

"In essence, it will be necessary to 'distance' the new products from the old one, while at the same time capitalizing on some of the positive features of Norplant: safety, acceptability/satisfaction and effectiveness," states Blumenthal.

Organon, which has launched Implanon in many European countries as well as in Australia and Indonesia, is developing programs to educate and train U.S. clinicians, states **Nancy Alexander**, PhD, director of contraception. **(See "Contraceptive implants: Single-rod Implanon headed to United States," *CTU*, June 2002, p. 61.)**

"We view this as an important and necessary effort so that those health care providers who will be offering the method are competent and proficient in both insertion and removal," reports Alexander. "We also are developing materials for potential patients so that they understand the advantages and drawbacks of this contraceptive choice."

Check insertion device

One of the real benefits of Implanon to the clinician and patient lies in its ease of insertion, says **Edio Zampaglione**, MD, Organon's associate director of contraception. No incision is necessary, and the average time for insertion is just over one minute, he reports. The key? Look to the disposable applicator, an insertion device with a beveled needle on one end in which the Implanon implant is preloaded. This eliminates any contact with the implant prior to insertion, thus minimizing the chance of contamination, says Zampaglione.

The needle is inserted at an approximate 20-degree angle in the upper inner arm between the biceps and triceps. Once the skin is penetrated, the clinician tents up the skin and gently advances the insertion device until the needle end is completely inserted. The opposite end of the device is turned about 90 degrees. The needle is gently withdrawn, resulting in the Implanon rod being left in the tunnel that was created by the needle, explains Zampaglione. After insertion, the clinician palpates Implanon to confirm correct placement, and the puncture site is covered with a butterfly bandage.

"The major differences between Implanon insertion and its predecessor are there is only one rod to insert, it comes preloaded in a disposable applicator device, and that no incision is necessary for insertion," he explains.

COMING IN FUTURE MONTHS

- Update on barrier methods
- Help prevent sterilization regret
- Teratogens and contraception — what you need to know
- New medications and instruments in abortion care
- Tips on talking to teens about contraception

The timeline for the U.S. introduction of the two-rod contraceptive implant has not been established, says Wyeth spokeswoman **Natalie de Vane**. The method was originally developed by the New York City-based research organization, the Population Council.

"At this time, we are currently working on plans to make the two-rod levonorgestrel implants available," she says. "This process involves several commercial and regulatory actions."

FDA approval for the two-rod implant was issued in 1996; however, it has not yet reached the U.S. commercial market. Marketed elsewhere as Jadelle, the method is approved for five years in Finland and other European countries, and it is approved for three years in Indonesia and Thailand. The FDA initially approved the two-rod implant for three years' use; in July 2001, the agency sent an approvable letter for extension of use to five years, according to the Population Council.

Norplant support on tap

What is Wyeth doing to support providers and women with Norplant implants? Wyeth issued provider letters on July 26, 2002, and stated that backup contraception is no longer needed for patients who were using Norplant kits from lots distributed beginning Oct. 20, 1999, with expiration dates in 2004. However, women who are using condoms for protection against sexually transmitted diseases should continue to use them.

In its communication, Wyeth included an information sheet that could be sent to women using the affected product to inform them that backup contraception was no longer necessary to prevent pregnancy. Wyeth will pay for backup, barrier, or other nonhormonal methods of contraception until Dec. 31, 2002.

In addition, health care providers and patients can call the toll-free Norplant System Information Line, (800) 364-9809, which operates weekdays during business hours, says de Vane.

Since Norplant will no longer be available, women will need to consider other contraceptive options as they approach the five-year expiration dates of their implants, according to information included in the July 26, 2002, letter. If patients would prefer to have the Norplant capsules removed, Wyeth will pay for removal procedures until Dec. 31, 2002, the letter states.

Remember that recently published research conducted in seven countries indicates that Norplant is safe and highly effective for seven years for women whose weight is less than 154 pounds, two years longer than the five-year period approved in the U.S. product labeling,[1] says **Anita Nelson**, MD, professor in the obstetrics and gynecology department at the University of California in Los Angeles (UCLA) and medical director of the women's health care clinic and nurse practitioner training program at Harbor-UCLA Medical Center in Torrance.

Reference

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Sterilization options may expand soon in U.S.

A Food and Drug Administration (FDA) advisory committee has recommended approval for Essure, an alternative to tubal ligation, developed by Conceptus of San Carlos, CA. The committee recommended that Essure be approved once certain conditions are met, which include changes to the labeling and implementation of the company's pre-existing plan to conduct post-marketing surveillance. While the committee's recommendation is not binding, it moves the investigational device a step further in the development pipeline. **(See "Noninvasive female sterilization eyed," *Contraceptive Technology Update*, February 2002, p. 15.)**

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A Food and Drug Administration advisory committee has recommended approval for Essure, a transcervical sterilization option developed by Conceptus. While the committee's recommendation is not binding, it moves the investigational device a step further.

- Compared with tubal sterilization, transcervical sterilization represents an easier, faster, and less-invasive procedure, requires less anesthesia, and results in less pain and a shorter recovery.
- Essure is available in Australia, Singapore, Canada, and several European markets. List price in Australia is about $600; in Europe, about $700.

The company is negotiating labeling with the FDA and awaiting its final decision, says **Stan Van Gent**, vice president of marketing for Conceptus.

A new alternative to tubal ligation could have a significant impact. Each year, more than 700,000 U.S. women opt for permanent surgical sterilization via tubal ligation.[1] Half of these procedures are performed postpartum, and half are performed as ambulatory interval (unrelated in time to a pregnancy) procedures.[1]

Review the benefits

There are many women who can benefit from less invasive, permanent contraception, says **Wayne Shields**, president and chief executive officer of the Washington, DC-based Association of Reproductive Health Professionals (ARHP). The Essure method represents another option in contraceptive choices, he notes.

Transcervical sterilization provides a good alternative to tubal sterilization, according to the ARHP, which hosted a December 2001 conference on the subject. **(A clinical monograph was published following the conference; see the resource box, above right, for details.)**

Although considered safe, tubal sterilization carries some risks, according to the ARHP.

Compared with tubal sterilization, transcervical sterilization is an easier, faster, and less-invasive procedure, requires less anesthesia, and results in less pain and a shorter recovery period — all significant benefits to the woman, physician, and insurers, states the ARHP.

"If we have, now, a transcervical method that is well tested and is highly effective and safe to provide, one that can be provided without trespassing in the peritoneal cavity and that does not require general anesthesia, women in the U.S. should have access to that method," states **Amy Pollack**, MD, MPH, president of the New York City-based EngenderHealth, a not-for-profit family planning and reproductive health organization. Pollack testified before the FDA advisory committee prior to its decision on the method.

Although female sterilization using laparoscopic and minilap approaches most often are provided using local anesthesia in developing countries, they almost exclusively are performed in the United States using short-acting general anesthesia, states Pollack. Data from the CREST (U.S. Collaborative Review of Sterilization) studies cite the use of general anesthesia as a predictor of complications in women undergoing interval tubal sterilization, she observes.

The Essure method calls for a soft micro-insert to be placed in the fallopian tube through the cervix using a minimally invasive transcervical tubal access catheter. Once in place, the device is designed to elicit tissue growth in and around the micro-insert to form an occlusion in the fallopian tube. An Essure procedure does not require cutting or penetrating the abdomen and can be performed in a less-costly setting without general anesthesia. A woman is expected to return home about 45 minutes after the procedure is completed, according to the company.

After 12 weeks, the woman is examined post-placement to confirm satisfactory micro-insert location. During the period before the placement is verified, the woman must use alternative contraception.

Phase II and pivotal trials were conducted in the United States, Australia, and Europe. A total of 130 women were included in the Phase II trial, with 518 women in the pivotal trial. To date, there have been no reported pregnancies, according to Conceptus. The company plans to submit its research data for publication, says Van Gent.

In unpublished one-year follow-up data on patients from the method's pivotal trial, 92% of patients who were employed returned to work in one day or less after the procedure day. Pivotal trial results also indicate that nearly 60% of patients were back to their regular physical activities within one day; and within two days, 77% had resumed regular activities.

RESOURCES

The Washington, DC-based Association of Reproductive Health Professionals (ARHP) has published an issue of its monograph, *Clinical Proceedings*, on the topic of transcervical sterilization. The monograph is based on a December 2001 ARHP conference, *Clinical Update on Transcervical Sterilization*. Review the monograph on-line at ARHP's web site, www.arhp.org. Click on "Publications," "*Clinical Proceedings*," then the publication title. Continuing education credits are available.

For more information on Conceptus, contact:

- **Conceptus**, 1021 Howard Ave., San Carlos, CA 94070. Telephone: (650) 802-7240. Fax: (650) 610-8363. Web: www.conceptus.com.

The Essure method is available in Australia, Singapore, Canada, and several European markets. While the U.S. cost has yet to be determined, list price in Australia is about $600; in Europe, the list price is about $700.[2]

As with other methods of sterilization, the Essure method represents a form of permanent birth control. Provider counseling is key to avoid patient regret, states Shields.

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2. Association of Reproductive Health Professionals. Clinical update on transcervical sterilization. *Clinical Proceedings* May 2002; 10. ■

EC access initiatives moving forward in U.S.

EXECUTIVE SUMMARY

With results from a just-published label comprehension study in hand, Women's Capital Corp. will seek over-the-counter status for its levonorgestrel-only emergency contraceptive pill (ECP) Plan B.

- The results of the study indicate that by reading the prototype label, most women could understand key information necessary for safe and effective use of the ECP.
- The company is promoting expanded EC access in Washington state with a media campaign. Women can obtain EC without advance prescriptions at 150 pharmacies.

Plans are on track to seek over-the-counter (OTC) status for the levonorgestrel-only emergency contraceptive pill (ECP) Plan B, with results from a just-published label comprehension study indicating that women can grasp the necessary information for safe and effective use of the drug.[1]

At *Contraceptive Technology Update* press time, officials with the Washington, DC-based Women's Capital Corp. were scheduled to meet with the Food and Drug Administration to review the company's support material prior to actual filing of the OTC application, reports **Sharon Camp**, PhD, company president and chief executive officer. If the material is in order, expect the application to be filed in October 2002, she says.

A pharmacokinetic study of adolescent use of Plan B has been completed, with blood sample analysis now under way, says Camp. A safety study of adolescent use is enrolling participants and is expected to finish soon, she notes. A large-scale behavioral study also is under way.

The label study was designed to evaluate women's comprehension of a prototype OTC package label for an ECP product.

To test the labeling, researchers conducted interviews with 663 women in malls and family planning clinics in eight U.S. cities. To be eligible for the study, women had to be 12-50 years old and able to read English well enough to read an OTC product label.

After looking at the package, women were asked 30 questions that addressed 11 communication objectives about indications, contraindications, instructions, side effects, and management of serious complications. Most questions asked whether use of the product would be appropriate in a described situation, such as the morning after a condom broke during sexual intercourse.

Seven of the 11 communication objectives were each understood by more than 85% of subjects. Most women in the study understood the most important objectives: The product is indicated for prevention of pregnancy after unprotected sex (93%); the first pill should be taken within 72 hours or as soon as possible after intercourse (97%); the product should not be used by women who already are pregnant (98%); and that the product does not prevent sexually transmitted diseases or HIV / AIDS (94%).

Researchers believe the results of the study demonstrate that women should be able to use EC safely and effectively if it were distributed over the counter, says **Elizabeth Raymond**, MD, MPH, associate medical director of the Biomedical Affairs Division of Family Health International in Research Triangle Park, NC. Raymond served as lead author of the study.

"The fact that so many of our study subjects understood the label is highly significant," she says. "It shows that just by reading the label, women can get the information they need to use the product properly. They don't need counseling by a clinician."

Researchers recently finished another study in which they evaluated how women actually did use a prototype OTC Plan B product; the results

of that study will be available in a few months, states Raymond.

Ads boost awareness

Women in Washington state now enjoy expanded access to EC through the 150 pharmacies that participate in the collaborative drug practice program under way in the state. **(See "Pharmacists, providers linking to provide emergency contraception," *CTU,* August 1999, p. 85.)** The program allows women to obtain EC through participating pharmacists without an advance prescription.

A 10-week media campaign now running on local radio stations and in area newspapers is reminding women of the pharmacy access program. The campaign should reach more than 5 million sexually active women ages 18-34 who are at risk for an unintended pregnancy, estimate Women's Capital Corp. officials.

The print ads contain the following message: "'Oops' and 'Uh-oh.' Two phrases that should never be uttered in a sexual context. Find out how Plan B, taken within 72 hours of intercourse, can be your backup plan in preventing pregnancy. And find yourself uttering phrases like 'Phew!' Accidents happen. That's why there's Plan B." Readers are then directed to the product's web site, www.go2planb.com; and a toll-free telephone hotline, (866) Turn2planB [(866) 887-6275], for more information. The hotline and web site provide full information on EC and a directory of Washington pharmacists who provide it on a walk-in basis. The radio ads convey a similar message about pharmacist availability of Plan B.

Pharmacists who participate in the EC program were alerted about the upcoming campaign so they could stock up on product, display patient brochures, and put up window posters to let women know about EC availability, Camp states.

"Too many women in Washington state still don't know what Plan B is or where to find it when they need it, and they don't have a lot of time to find out," says Camp. "We want to help close the information gap so more women can actually get access to Plan B within 72 hours."

Reference

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Standard Days Method: Family planning option

For couples who want a contraceptive method that is user-controlled and free from side effects, a new fertility awareness-based form of family planning may be a suitable option for them.

Based on sophisticated computer modeling of reproductive physiology data, the Standard Days Method (SDM) identifies the 12-day "fertile window" of a woman's menstrual cycle. The 12 days take into account the life span of the woman's egg, the viable life of sperm, as well as the variation in the actual timing of ovulation from one cycle to the next.[1-3] The method calls for users to avoid unprotected intercourse during cycle days eight through 19, during which time they can protect against the risk of pregnancy through the use of contraception, such as condoms, or abstinence.

A two-year clinical trial evaluated the effectiveness of the method for 478 women in Bolivia, Peru, and the Philippines, all of whom were of childbearing age with menstrual cycles between 26 and 32 days long.[4] The study followed the women over 13 cycles. A life table analysis of the data indicates a cumulative probability of pregnancy of 4.75% over 13 cycles of correct use of the method, and an 11.96% probability of pregnancy under typical use.

The pregnancy prevention offered by the method and its acceptance by couples in a wide range of settings make it a viable option in family planning, says study co-author **Victoria Jennings**, PhD, director of the Institute for Reproductive Health and

EXECUTIVE SUMMARY

A new fertility awareness-based form of family planning now is available: the Standard Days Method.

- Based on sophisticated computer modeling of reproductive physiology data, the method identifies the 12-day "fertile window" of a woman's menstrual cycle.
- The method calls for users to avoid unprotected intercourse during cycle days eight through 19, during which time they can protect against the risk of pregnancy through use of contraception, such as condoms, or abstinence. Researchers have developed CycleBeads, a string of 32 color-coded beads with each bead representing a day of the menstrual cycle. They help women keep track of which days to avoid unprotected intercourse.

professor of obstetrics and gynecology at Georgetown University, both in Washington, DC.

"While we are glad to see that there are some new delivery systems, such as the patch and the ring, for hormonal methods, as well as developments such as the female condom, we realize that most providers and programs do not offer a natural method," says Jennings. "We wanted to help fill that gap."

Not rhythm method

Providers may look at the SDM as a form of the rhythm method, but there is a difference, explains Jennings. The rhythm method requires a woman to collect detailed information about the last six menstrual cycles and perform monthly calculations to figure out which days in the current cycle she is most likely to get pregnant, she notes. The SDM requires no such calculations by the user. In addition, no reliable, scientific effectiveness trial of the rhythm method has been reported.

To develop the SDM formula, researchers used a large data set from the Geneva-based World Health Organization, which includes information on more than 7,500 menstrual cycles from women in five countries.[5] Information about the variable probability of pregnancy on different cycle days relative to ovulation also was considered in the analysis.

The researchers found that women who usually have menstrual cycles between 26 and 32 days long have a significant probability of pregnancy if they have unprotected sex on days eight through 19 of their cycles, says Jennings. On other cycle days, the probability of pregnancy is extremely low.

To help women keep track of which days to avoid unprotected intercourse, the Institute for Reproductive Health developed CycleBeads, a string of 32 color-coded beads with each bead representing a day of the menstrual cycle. Beginning with the red bead, which represents the first day of her menstrual period, the woman moves a small rubber ring one bead each day. Brown beads designate the days when pregnancy is very unlikely, and glow-in-the dark white beads (beads eight through 19) represent fertile days. CycleBeads serve three primary functions, according to Jennings:

- The beads help keep track of a woman's cycle days. By moving the rubber ring one bead per day, beginning with the first day of her menstrual cycle, the user can see where she is in her cycle.
- The different colors of the beads help the woman determine the days pregnancy is likely if she has unprotected intercourse, and which days pregnancy is unlikely.
- By looking at the "darker" bead and the total number of beads, a woman can easily tell whether her cycle is between 26 and 32 days long, the optimal cycle range for using the SDM.

"CycleBeads are a critical tool for teaching, learning, and using the SDM," says **Marcos Arevalo**, MD, director of clinical trials at the Institute for Reproductive Health and assistant professor of obstetrics and gynecology at Georgetown University. "The fact that they are visual and easy to understand makes them ideal for clients and providers in a wide range of settings."

Roberto Rivera, MD, director of the Office of International Research Ethics at Family Health International in Research Triangle Park, NC, says he has seen the Standard Days Method presented in the field, and the CycleBeads necklace has facilitated the use of the method. It offers a practical way for the woman or for the couple to find out when the fertile days start (to avoid unprotected intercourse), and it indicates very clearly when the fertile days are finished, he observes.

In addition, CycleBeads are an excellent tool for promoting communication between the woman and her partner, not only about method use and how they choose to deal with the days in her cycle when pregnancy is likely, but also about family planning issues as well, notes Jennings.

Correct use essential

Negotiation is a key factor in using any form of natural family planning, observes Rivera. Such methods are not woman-controlled; they involve the partner as well, he notes. If the partner does not cooperate, it is difficult to use the method correctly and consistently, he points out.

In discussing SDM along with other contraceptive options, providers will need to review the efficacy rates for each method, says Rivera. Couples who are seeking very reliable contraception but may have difficulty using SDM correctly all of the time should consider alternate methods. However, SDM may be an appropriate choice for couples motivated to use such a fertility awareness-based method.

"I'm a strong believer that there is no one method that is good for all couples, and that the secret of family planning is to be able to find for the woman, or the couple, the method that is best," Rivera notes.

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Use resources to teach Standard Days Method

The Washington, DC-based Institute of Reproductive Health is working on several levels to help providers become proficient in teaching the Standard Days Method (SDM) to women, reports **Victoria Jennings**, PhD, institute director. With support from the U.S. Agency for International Development, the institute is educating trainers in several countries around the world, and has developed and tested materials that can be adapted to many settings. Training curricula ranges from a three-hour training for health professionals to a two-day training for community-level personnel.

Existing natural methods of family planning are simply too complex and time-consuming for most programs to offer and most clients to learn and use, says Jennings. The SDM offers a new option, she adds.

"Despite the great efforts of many dedicated people over the past two decades, the numbers of users of these methods, such as the Billings Method and the Symptothermal Method, remain low," states Jennings. "We needed something that was program-friendly, provider-friendly, and user-friendly."

Choose from options

The institute makes the following resources available for providers interested in offering the SDM:

• **CycleBeads:** CycleBeads are distributed with a package insert that guides users through all the steps required to determine whether the method is appropriate for them. It also explains how to use CycleBeads and provides answers to frequently asked questions. The material is available in English, Spanish, and French. *(Editor's note: The beads are available on-line at www.cyclebeads.com. For more information about ordering CycleBeads, send an e-mail to info@cyclebeads.com or write to: Cycle Technologies, 467 Central Park W., Suite 4B, New York, NY 10025. Price varies by number ordered.)*

• **Introductory CD-ROM:** The CD-ROM explains how the SDM was developed and tested and how to use CycleBeads. It also provides a checklist for screening potential users and responses to frequently asked questions. It is available in English and Spanish. Price is $5, plus $2 shipping and handling; see order information listed below.

• **Video or CD-ROM:** "CycleBeads: an Easy Way to Use the Standard Days Method." This five-minute audiovisual is appropriate for providers and clients. It emphasizes the importance of informed choice and shows how the method is being used in diverse settings. It also explains how to use CycleBeads. It is available in English. Price is $5 plus $2 shipping and handling; see order information listed below.

• **Counseling Guide:** This comprehensive guide for providers explains how to appropriately counsel women and couples on the SDM using CycleBeads. The guide describes for whom the SDM is most appropriate and the key aspects covered in a counseling session. It directs the provider through the counseling process in an interactive and easy-to-read format. It is available in English, Spanish, and French. Price is $15 plus $2 shipping and handling. See order information listed below.

• **Brochure:** This informative brochure explains the SDM, how to use it, and its advantages and disadvantages. It includes a self-assessment for the reader to determine if the method is appropriate for her and addresses some frequently asked questions. It is available in English and Spanish. The brochure is free.

• **Training Program:** The Institute for Reproductive Health conducts training programs for trainers and service providers. Training programs include participant materials, a pre-training assessment plan, and pre- and post-training consultation with participants. Participant materials include a counseling guide, job aids, a CD-ROM, and samples of CycleBeads. Contact the institute at irhinfo@georgetown.edu, or call (202) 687-1392.

Training is available in English, Spanish, and French. Price varies by location, length of training, and number of participants.

• **Training Manual:** The manual guides trainers through the process of training providers in the SDM, using CycleBeads. It includes information for designing, conducting, and evaluating training programs, and it addresses issues critical to the successful use of the method, such as the couple's relationship and gender issues. The content can be adapted to all types of providers, ranging from clinicians to community personnel with limited knowledge of reproductive health and family planning. It is available in English, Spanish, and French. The manual is available to training programs, following consultation with the institute. Price is $45 plus $5 shipping and handling; see order information listed below.

• **Distance Training Package:** The distance-training package is for providers who are not able to participate in a formal training program. It consists of a pre-test and post-test, a CD-ROM with an overview of the SDM, an explanation of how to use CycleBeads, a checklist for screening potential users, a counseling guide, an introductory video and CD-ROM, and a series of case studies. It is available in English, Spanish, and French. The package is available to training programs or providers, following consultation with the institute. Price is $75 plus $5 shipping and handling; see order information listed below.

Check order information

Unless otherwise noted, all resources are available from the Institute for Reproductive Health and can be ordered on-line at www.irh.org, via e-mail at irhinfo@georgetown.edu, by fax at (202) 537-7450, or by mail at: Institute for Reproductive Health, 4301 Connecticut Ave. N.W., Suite 310, Washington, DC 20008. Institute materials are available at no cost to selected organizations that support family planning and reproductive health programs in developing countries. Prices given are for organizations in developed countries only. Checks are payable to DGI/IRH. Allow 4-6 weeks for delivery. ■

Answers to questions on DMPA, HPV testing

[Editor's note: Contraceptive Technology Update *readers have questions, and members of the CTU Editorial Advisory Board have the answers. Commenting this month are* ***Andrew Kaunitz****, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center/Jacksonville, and* ***Sharon Schnare****, RN, FNP, CNM, MSN, women's health consultant and clinician with the Seattle King County Health Department in women's and adolescent health care and the International District Community Health Center in Seattle. (Readers can submit questions either through the CTU web site, www.contraceptiveupdate.com; or by mailing "Ask the Experts,"* Contraceptive Technology Update, *P.O. Box 740056, Atlanta, GA 30374.)]*

Question: The time frame given for Depo Provera (depot medroxyprogesterone acetate, DMPA, Phar-macia Corp., Peapack, NJ) injections in *A Pocket Guide to Managing Contraception* (Bridging the Gap Foundation, 2001) is 11-13 weeks. Is there any latitude in this time frame so the drug may be given at 10 weeks? If so, is there a reference in the literature to substantiate the shorter time frame?

Kaunitz: The recommended reinjection schedule for DMPA injections is every 12 weeks or three months. Earlier reinjection (e.g., eight to 11 weeks following the prior injection) for convenience reasons is perfectly appropriate. Indeed, substantial and reassuring experience with doses and schedules higher and more frequent than 150 mg every 12 weeks exists in clinical settings, including treatment of endometrial and breast neoplasia as well as for other conditions. Clinicians and users, however, should be aware that regular administration of DMPA at intervals of fewer than 12 weeks can increase the likelihood of such side effects as increased appetite and bloating.

Schnare: The reason DMPA is given at 11-13 weeks is because this schedule provides the highest effectiveness of the contraceptive; although the contraceptive levels are maintained for up to 14 weeks in most women.[1,2,3] It has been standard practice in many clinics to provide DMPA as early as 10 weeks, based on patients' requirements or request. For example, women leaving for vacations may need to have their injection given earlier. Use of early injection has been studied. A study by Harel et al. showed that giving

DMPA earlier did not affect bleeding patterns in adolescents.[4]

Question: I am an OB/GYN at a university student health center. Since the release of the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines on management of women with cytological abnormalities, I have continued to read articles and have been trying to decide the best course of action when caring for college women. We do have liquid Pap tests available to us. Normally, we proceed directly to colposcopy for low-grade squamous intraepithelial lesion and high-grade squamous intraepithelial lesion Pap tests. We have been repeating atypical squamous cells of undetermined significance (ASC-US) Paps in six months. Do you think college-aged women with ASC-US Paps should have human papillomavirus (HPV) reflex testing? Cost is always a concern for the students.

Schnare: The answer is multifaceted: 1) No, you do not need to do liquid-based reflex HPV testing on women with ASC-US; you may repeat the Pap in four months, unless the woman is at high risk for dysplasia (HIV-positive or has AIDS; previous abnormal Paps; history of cryotherapy or loop electrosurgical excision; or multiple sex partners, especially with men whose previous partners have cervical dysplasia or cancer.) Remember that women who smoke also increase their risk of cervical dysplasia — perhaps doubling their risk. 2) Research has shown that doing the reflex HPV typing is more cost-effective than repeat Paps[5]; however, if your students receive their care for free, but must pay for their Paps, then to the student, it is more costly. **(*CTU* covered the new ASCCP guidelines in its article, "Improve cervical cancer screening: Review new terminology, guidelines," July 2002, p. 73. To review the guidelines, visit the ASCCP web site: www.asccp.org.)**

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CTUPDATES
News ■ Resources ■ Events

Get new fact book on sterilization

Voluntary sterilization remains the most prevalent form of contraception worldwide, according to *Contraceptive Sterilization: Global Issues and Trends*, a new book from New York City-based EngenderHealth.

According to EngenderHealth, approximately 222 million women and men of reproductive age are protected from unintended pregnancy by sterilization. Since 1985, the number of countries restricting access to medical sterilization procedures has declined by almost 75%, from 28 to eight.

Edited by Evelyn Landry, the fact book includes coverage of such topics as high-quality service delivery, who uses sterilization and why, laws and policies around the world, key factors influencing the use and outcomes of permanent contraception, overviews of female and male options, research gaps, and projections of future needs.

The book can be downloaded from the EngenderHealth web site. Go to www.engenderhealth.org/sterilization. It also may be ordered in print form by contacting the EngenderHealth Material Resources department at 440 Ninth Ave., New York, NY 10001. Telephone: (212) 561-8000. Fax: (212) 561-8067. E-mail: materialresources@engenderhealth.org. ▼

Designer pill packs are now available

Women now can carry their oral contraceptives in style with the introduction of two limited edition compact pill packs created by fashion designer Nicole Miller.

The two styles, Zebra Kiss and Red High Heels,

now join the line of Personal Pak tablet dispensers designed to carry Ortho Tri-Cyclen pills (Ortho-McNeil Pharmaceutical, Raritan, NJ). Other pack designs include Leopard Print, Fuchsia Daisy, Lapis, and Onyx.

Each compact costs $4.95 plus $1.50 shipping, and can be ordered by calling (866) 221-1031. The packs also can be ordered on-line at www.ortho tri-cyclen.com to receive $1 off purchase. ▼

NPWH accreditation program gets DOE nod

The Washington, DC-based National Association of Nurse Practitioners in Women's Health's Program for Accreditation has been recommended for continued recognition by the U.S. Department of Education (DOE) National Advisory Committee on Institutional Quality and Integrity.

The program was established to help ensure that the education of women's health nurse practitioners meets national standards of quality as well as to encourage the availability of qualified nurse practitioners. It was first recognized by the DOE in 1996 as an accrediting agency for women's health nurse practitioner programs located within the United States and its territories. ■

CE objectives

[For details on *Contraceptive Technology Update*'s continuing education program, contact: Customer Service, American Health Consultants, P.O. Box 740056, Atlanta, GA 30374. Telephone: (800) 688-2421. Fax: (800) 284-3291. E-mail: customerservice @ahcpub.com. Web: www.ahcpub.com.]

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

- State the key message contained in the July 26, 2002 health care provider letter issued by Wyeth Pharmaceuticals regarding Norplant use. **(See "Don't count implants out: 2 options may take Norplant's place" in this issue.)**
- Cite which statement does not describe the Essure permanent birth control method now under investigation in the U.S. **(See "Sterilization options may expand soon in U.S.")**
- Give the name of the fertility awareness method that identifies the 12-day "fertile window" of a woman's menstrual cycle **(See "Standard Days Method: Family planning option.")**
- State the subtypes of the HIV virus being targeted in the U.S. trial of the AIDSVAX vaccine. **(See "HIV vaccines: New generation may reduce transmission of virus.")** ■

Contraceptive Technology Update® (ISSN 0274-726X), including **STD Quarterly**™, is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Contraceptive Technology Update**®, P.O. Box 740059, Atlanta, GA 30374.

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CE/CME Questions

CME subscribers: Please save your issues in order to take the CME semester tests in June and December. A Scantron will be inserted in those issues, but the questions will not be repeated.

13. What was the key message contained in the July 26, 2002, health care provider letter issued by Wyeth Pharmaceuticals regarding Norplant use?
A. Women who use Norplant must continue to use backup contraception following tests showing that suspect lots have less-than-effective dosages of the drug.
B. Women who use Norplant no longer need a backup, barrier, or other nonhormonal method of contraception, following tests showing that suspect lots of the implant system have been found effective.
C. Women who use Norplant should have the implants immediately removed due to safety issues due to increased risk of stroke.
D. Women who use Norplant can safely rely on its contraceptive effectiveness for up to 10 years.

14. Which statement does *not* describe the Essure permanent birth control method now under investigation in the United States?
A. The Essure procedure does not require cutting or penetrating the abdomen.
B. The Essure procedure can be performed in a less-costly procedure setting without general anesthesia.
C. A woman is expected to return home about 45 minutes after the Essure procedure is completed.
D. The method provides immediate contraceptive efficacy following placement of the Essure device.

15. What is the name of the fertility awareness method that identifies the 12-day "fertile window" of a woman's menstrual cycle?
A. Standard Days Method
B. Basal Body Temperature Method
C. Billings Method
D. Ogino-Knaus Method

16. What subtypes of the HIV virus are being targeted in the U.S. trial of the AIDSVAX vaccine?
A. Subtype C
B. Two strains of subtype B
C. Two strains of subtype E
D. Subtypes B and E

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S·T·D QUARTERLY™

HIV vaccines: New generation may reduce transmission of virus

Prevention efforts must continue to stem spread of disease

Every day, the statistics mount in the AIDS epidemic. According to the Joint United Nations Programme on HIV/AIDS, an estimated 14,000 people worldwide become infected with HIV each day, with more than half of new infections occurring in young people younger than age 25. How will the epidemic be stemmed?

Look to progress on the HIV vaccine front. Two vaccines are in advanced clinical trials, and increased federal funding has expanded the research pipeline by allowing for more exploration of various vaccine strategies. According to the federal National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH), six potential HIV vaccines were tested during the past five years in 12 small-scale clinical trials conducted in the United States and around the world. During the next two years, more than a dozen potential vaccines are expected to be ready for testing. They will require more than 20 clinical trials of various sizes.

Look to 2003 for results to be reported from the advanced clinical trials, says **Jorge Flores**, MD, chief of the Vaccine Clinical Research Branch of the NIH's Division of AIDS. Both trials involve the AIDSVAX vaccine developed by Brisbane, CA-based VaxGen. The first trial involves 5,400 participants in North America, Puerto Rico, and the Netherlands, with the bivalent vaccine targeting two strains of HIV subtype B, found predominately in North America, Western Europe, Australia, New Zealand, and parts of South America. The study is scheduled to conclude at the end of 2002.

A second trial among 2,500 participants is taking place in Bangkok, Thailand, using a vaccine formulation designed to protect against the two predominant strains found in Southeast Asia and the Pacific Rim, subtypes B and E. Results of the Thailand study are expected to be available in the fourth quarter of 2003.

"In addition to these trials, we have multiple other studies going on, including Phase II trials," says Flores. "Four or five years from now, there will be five to six efficacy trials for different vaccines."

The vaccine formulations AIDSVAX B/B and AIDSVAX B/E are made from a synthetic clone of a protein found on the surface of HIV, gp120.

EXECUTIVE SUMMARY

Two HIV vaccines are in advanced clinical trials, and increased federal funding has expanded exploration of vaccines.

- Look to 2003 for results from the advanced clinical trials, which are testing the AIDSVAX vaccine developed by VaxGen. The first trial, conducted in North America, Puerto Rico, and the Netherlands, is examining a bivalent vaccine targeting two strains of HIV subtype B. The second trial, conducted in Bangkok, Thailand, uses a vaccine formulation targeting HIV subtypes B and E.
- Researchers says prevention messages must continue to be emphasized to stem the AIDS epidemic.

Using recombinant DNA technology, the gene for gp120 is cloned and then duplicated by Chinese hamster ovary cells in commercial-scale fermenters. The gp120 then is purified and mixed with alum, an adjuvant that boosts the immune response, to create the vaccine.

When the trials are concluded, researchers will determine whether the immune system response induced by AIDSVAX reduces the amount of HIV to undetectable levels in vaccinated volunteers who became infected with HIV after receiving the vaccine, or lowers the amount of virus in the bloodstream to detectable but manageable levels. Either of these potential outcomes could represent a significant breakthrough by potentially helping HIV-infected people live longer and reduce their ability to infect others. It is not yet known whether either of these outcomes, known as secondary endpoints, would be considered for regulatory approval.

More vaccines on way

A new generation of T cell-based HIV vaccines also offers promise in delaying the onset of AIDS symptoms and reducing transmission of the virus. These vaccines have the potential to significantly impact the epidemic if they are shown to reduce the infectiousness of infected individuals for a prolonged period of time, says **Lawrence Corey**, MD, the principal investigator of the HIV Vaccine Trials Network, an international collaboration of scientists and institutions with headquarters at The Fred Hutchinson Cancer Research Center in Seattle.

T cell-based vaccines work differently from traditional vaccines as they work later and are aimed at controlling viremia and decreasing the viral load so that transmission can be reduced, explains Corey. These vaccines could significantly postpone development of HIV in infected individuals, he notes.

"It is also encouraging that cross-clade T cell responses to HIV are being achieved at high frequency with many of the T cell vaccines currently in clinical trials," says Corey. "Cross-clade responses to a potent vaccine may provide more efficacy than clade-specific responses to a weak vaccine, opening the door to economies of scale and global manufacture of a single vaccine."

Whether HIV vaccines prove to prevent infection or delay illness, researchers agree that a strong prevention message must continue to be emphasized in the battle against HIV/AIDS.

"People will still expose themselves to the risk of HIV infection, so we will have to continue fighting with whatever other measures that can protect people from that exposure, be it behavioral interventions, education, counseling, or other measures that prevent transmission," says Flores.

There is a natural tendency for people to think that once they are protected against disease to take risks, notes Flores. To prevent against this tendency, providers must help in changing behavior through education and counseling.

Eventually scientists will develop vaccines that are 100% effective, says Corey. However, it appears that the initial vaccines will not meet that goal, and mathematical modeling indicates a partially effective vaccine can be overwhelmed, he notes. An effective prevention and treatment program can aid in the fighting the battle, he notes.

"Vaccine deployment must take place within the context of a larger HIV prevention and treatment effort if we are to stem the tide of this pandemic," he states. ■

Test for STDs from single Pap specimen

Clinicians now can monitor for cervical lesions, as well as human papillomavirus (HPV), chlamydia, and gonorrhea infection, using a single ThinPrep Pap Test specimen. The Food and

EXECUTIVE SUMMARY

The Food and Drug Administration has approved testing for chlamydia and gonorrhea directly from an endocervical sample obtained from Cytyc Corp.'s ThinPrep Pap Test.

- Laboratories can use the sample obtained during the cervical exam to screen for the two diseases using Roche Diagnostic Corp.'s COBAS Amplicor automated system. This system eliminates the need for an additional sample.
- Providers are performing more chlamydia tests following the U.S. Preventive Services Task Force's 2001 recommendation that all sexually active women ages 25 and younger be screened routinely.

Drug Administration (FDA) recently approved testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* directly from the ThinPrep Pap Test collection vial using the COBAS Amplicor automated system developed by Basel, Switzerland-based Roche Diagnostics Corp.

One specimen yields several screens

About half of U.S. providers currently use the ThinPrep technology for Pap tests, estimates **Jeff Keene**, corporate spokesman for manufacturer Cytyc Corp. of Boxborough, MA. Cytyc gained FDA approval for the liquid-based ThinPrep Pap Test in 1996, with HPV testing approval awarded in 1997. With one collection medium, clinicians can take a single endocervical sample with the ability to run several screens on the specimen, he explains.

Providers are performing more chlamydia tests following the U.S. Preventive Services Task Force's 2001 recommendation that all sexually active women ages 25 and younger be routinely screened for the sexually transmitted disease (STD). **(See "Task force calls for chlamydia screening," *Contraceptive Technology Update,* July 2001, p. 81.)**

The task force recommendation calls for all women to be routinely screened for chlamydia if they:

- are sexually active and age 25 or younger;
- have more than one sexual partner, regardless of age;
- have had a STD in the past, regardless of age;
- do not use condoms consistently and correctly, regardless of age.

Chlamydia screening of sexually active young women ages 15-25 now is one of the performance measures included in the Washington, DC-based National Committee for Quality Assurance's Health Plan Employer Data and Information Set (HEDIS). HEDIS is the most widely used system for assessing managed care performance. The performance measure was added in 2000. **(Read about the addition of the performance measure in the February 2000 *CTU* article, "Women's health issues included in managed care report card," p. 17.)**

Review the research

Scientists conducted a prospective study to determine whether the automated COBAS Amplicor test could detect *Chlamydia trachomatis* in cervical specimens collected in the PreservCyt transport medium used in the ThinPrep Pap Test.[1] A total of 1,000 cervical specimens were collected from young women during routine Pap smear tests. Only specimens with normal cytology and in which the gynecologist found no clinical evidence of urogenital infections were selected.

The samples were stored in PreservCyt transport medium, then tested for chlamydial infection. To confirm the positive samples, the test was repeated on new endocervical swab specimens collected in transport medium used in the COBAS Amplicor test. Results indicated that the ThinPrep Pap Test may enable providers to monitor for cervical lesions and chlamydial infection with a single endocervical infection.

Tests uncommon in Title X clinics

While the ThinPrep Pap Test is fast becoming the standard of care in private providers' offices, it is rare in use as a first-line primary screen in federally funded Title X clinics due to costs, says **Judith DeSarno**, chief executive officer of the Washington, DC-based National Family Planning and Reproductive Health Association (NFPRHA). If the technology is employed, it is used as a secondary screen after an abnormal conventional Pap smear; even then, less than half of Title X clinics are able to use the technology, she notes.

An informal survey at the organization's recent annual meeting shows that almost no clinics are performing routine HPV screens from the ThinPrep technology. The ability to perform HPV screens from a ThinPrep sample can be useful, since newly released guidelines allow laboratories to test ASC-US (atypical squamous cells of undetermined significance) liquid-based samples used for the original Pap test for HPV, which eliminates the need for a repeat provider visit.[2] 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

RESOURCE

- **Cytyc Corp.**, Customer Service, 85 Swanson Road, Boxborough, MA 01719. Telephone: (800) 442-9892. Fax: (978) 635-1021. Web: www.thinprep.com.

that they simply need regular Pap tests. Women who are HPV-positive are identified and scheduled for further evaluation. **(Read more about the new guidelines in the July 2002 *CTU* article, "Improve cervical cancer screening: Review new terminology, guidelines," p. 73.)**

DeSarno says that while Cytyc Corp. is working with NFPRHA in exploring cost alternatives for the collection technology, clinics still have to pay the higher lab costs for processing the ThinPrep samples. Since clinics have been unable to afford the ThinPrep Pap Tests, it is doubtful they will be able to take advantage of the "one-stop" specimen testing for HPV, chlamydia, and gonorrhea.

"I think this is a giant leap forward in sort of a one-stop for a Pap test," she says. "I think there are some hard decisions down the road for Title X clinics."

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Clinical trials harmed by lack of informed consent

The mention of clinical trials often triggers a silence between physician and patient, usually because neither one knows much about the subject. Nearly 80% of physicians admit they would like to know more about clinical trials so they can help their patients make an informed decision before volunteering to participate.

"Most subjects enrolled in clinical studies have a meager understanding of what they have gotten into," says **Alan Sugar**, MD, chairman, New England Institutional Review Board and professor of medicine at Boston University School of Medicine. "Informed consent has largely focused around the signed form and has not practically become the continuous process that it needs to be. As a result, a subject's misunderstandings largely go unchallenged."

Properly informing patients is not only ethically necessary, say clinical trials experts, but it also ensures better trials and data. Last year, more than 17 million people seriously thought about participating, but only a few million actually completed their trials. And even among them, many gave their consent without a thorough knowledge of the facts. Indeed, patients can be so daunted by questions and lack of information that they simply decide not to volunteer.

"There's a simple ethical mandate that you don't ordinarily do dangerous things to people without their knowledge and consent," says **Dale E. Hammerschmidt**, MD, FACP, associate professor of medicine and director of Education in Human Subjects' Protection for the University of Minnesota Medical School in Minneapolis. "From a more pragmatic perspective, a well-informed subject is likely to cooperate better with the trial and is more likely to report potential problems. The quality of the data and the safety of the trial are both enhanced when the subjects really know what's going on."

Guide examines clinical trials

A new resource, written for doctors and clinical trial participants, can help answer some of these tough questions. Boston-based CenterWatch, the leading publisher of clinical trial news and information, now offers *Informed Consent*, a guide to the risks and benefits of volunteering for clinical trials.

Informed Consent is a step-by-step guide that begins with a history of the clinical trials industry, explores the drug development process, and how a new drug makes its way to the marketplace. It also details why people decide to participate, how to find clinical trials, how to research clinical trials and evaluate their risks, how to ensure proper informed consent, what the vulnerable populations are, and what to do when things go wrong. Cost is $16.95, and can be ordered from CenterWatch at (800) 765-9647, or by faxing (617) 856-5901. It also can be ordered through www.centerwatch.com; www.amazon.com; and www.barnesandnoble.com. ■