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INSIDE

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Rapid HIV testing method approved — prepare now to apply new strategies

New test yields results with 99.6% accuracy in as little as 20 minutes

How many times have you tested patients to determine their HIV status, never to see them return for the test results? Get ready for that scene to change; the Food and Drug Administration's (FDA) recent approval of a new test designed to detect HIV-1 antibodies in fingerstick whole blood samples will allow you to deliver the results in about 20 minutes.

About 2.1 million HIV tests are conducted each year as part of publicly funded counseling, testing, and referral programs.[1] According to Atlanta-based Centers for Disease Control and Prevention's (CDC) data, 30% of people who tested HIV-positive during 2000 and 39% of persons who tested HIV-negative did not return for their test results.[1]

The approval of a rapid HIV test has the potential to significantly impact the U.S. epidemic, says **Robert Janssen**, MD, director of the CDC Division of HIV/AIDS Prevention. The FDA approved the OraQuick Rapid HIV-1 Antibody Test, manufactured by OraSure Technologies of Bethlehem, PA, in November 2002.

"Availability of a rapid test will increase the number of infected people who know their status — a key goal of CDC's HIV prevention strategic

EXECUTIVE SUMMARY

Federal approval has just been given to the Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, PA). The test, designed to detect HIV-1 antibodies in fingerstick whole blood samples, will provide test results in about 20 minutes.

- While more than 60 rapid HIV tests have been developed and used in various countries, only two have received U.S. approval prior to OraQuick: Recombigen HIV-1 LA, which was withdrawn from the U.S. market due to poor performance, and Single Use Diagnostic System for HIV-1 (or SUDS, marketed by Abbott-Murex, Norcross, GA), which still is available.
- SUDS requires serum or plasma for analysis.

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plan — and likely will reduce the number of people who get tested but don't return for their results," states Janssen.

Shipments on the way

While more than 60 rapid HIV tests have been developed and used in various countries, only two have received approval from the FDA prior to OraQuick: Recombigen HIV-1 LA, which was withdrawn from the U.S. market due to poor performance, and Single-Use Diagnostic System for HIV-1 (or SUDS, marketed by Abbott-Murex, Norcross, GA), which still is available.[2] ***(Contraceptive Technology Update* reported on the SUDS test in the June 1998 article, "New guidelines open door for rapid HIV screening," included on p. 1 of the *STD Quarterly* inserted in the newsletter.)**

U.S. public health officials have been interested in bringing more quick, easy-to-use tests to market; the U.S. military, in particular, wants rapid tests to prevent the accidental transfusion of HIV-infected blood on the battlefield.[3]

At press time, shipments of the new test were scheduled to be under way, according to **William Bruckner**, OraSure vice president of strategic marketing. The company swung into production soon after the FDA approval. OraSure has entered in a coexclusive agreement with Abbott Park, IL-based Abbott Laboratories to distribute the OraQuick test. Abbott is focusing on hospital and physicians' office laboratory markets, while OraSure is working with the public health and criminal justice markets where it already maintains a direct sales force.

Pricing for OraQuick is going to be comparable to current lab-based tests, states Bruckner.

"Our intention is to make OraQuick as available as possible to as many certified outlets as possible within the United States," says Bruckner. "We want to get it in the hands of the people where it will do the most good."

Status of CLIA waiver?

The test has been categorized as "moderately complex" under the federal Clinical Laboratory Improvement Amendments of 1988 (CLIA) legislation, which specifies that laboratory requirements be based on the complexity of the test performed. SUDS also is rated as a moderate-complexity rapid HIV test; however, it requires serum or plasma as opposed to fingerstick whole blood for analysis.[4]

RESOURCES

- For more information on the **OraQuick Rapid HIV-1 Antibody Test,** contact: OraSure, 150 Webster St., Bethlehem, PA 18015. Telephone: (800) ORASURE (672-7873). Web: www.orasure.com.
- Review the Atlanta-based **Centers for Disease and Control Prevention's updated guidelines on HIV testing** at its web site: www.cdc.gov/hiv/testing.htm.
- Check out **counseling protocol information at the Project Respect-2 web site:** www.cdc.gov/hiv/projects/respect-2/default.htm.
- Review the **application and state agency contact information for Clinical Laboratory Improvement Amendments of 1988** certification at the Baltimore, MD-based Centers for Medicare & Medicaid Services web site: www.cms.hhs.gov/clia. Information about enrollment and the requirements for moderate-complexity testing are available at www.phppo.cdc.gov/clia/default.asp.

The test's moderate complexity designation means that the OraQuik test only can be performed in CLIA-approved labs by CLIA-certified laboratory technicians or medical staff. Administration of the CLIA program is handled by the Baltimore-based Centers for Medicare & Medicaid Services. **(See the resource box, above, for more information on CLIA certification.)** According to OraSure, there are nearly 40,000 qualified locations in the United States certified to perform moderately complex diagnostic tests; an estimated 17 million HIV tests are conducted annually at these locations.

To further broaden OraQuick's use in the fight against HIV, public health officials, including Health and Human Services Secretary Tommy Thompson, have called for the manufacturer to apply a CLIA waiver for the test. If the waiver is received, OraQuick can be used in such settings as outreach clinics and mobile vans. OraSure has filed a draft protocol with the FDA for the waiver and hopes to complete all necessary documentation in the next few months, Bruckner confirms.

Look at the results

According to data submitted by OraSure for FDA approval, the sensitivity of OraQuick in the clinical studies performed was 99.6% (95% confidence interval [CI] = 98.5%-99.9%), and specificity was 100% (95% CI = 99.7%-100%).[4] Such sensitivity and specificity make the test comparable to FDA-approved enzyme immunoassays in widespread use.[4]

If a negative test result is received, providers can offer those results at the initial visit, and no retesting is required. If the patient has a recent history (within three months) of known or possible exposure to HIV, the CDC recommends retesting since there may have been insufficient time for the development of detectable antibodies. All reactive (preliminary positive) rapid test results should be confirmed by supplemental testing by a Western blot or immunofluorescence assay.[5]

To perform the OraQuick test, a fingerstick sample of blood is collected and transferred to a vial, where it is mixed with a developing solution. The test device, which resembles a dipstick, is inserted into the vial. If HIV-1 antibodies are present in the solution, the device will display two reddish-purple lines.

For those living with HIV, knowledge of status is critical, but only 75% of those infected in the United States are aware of their infection, says Janssen. Because of the potential public health benefits of rapid HIV testing, the CDC and the Centers for Medicare & Medicaid Services are working with state and other health officials to make the test widely available and offer technical assistance and counseling training for its use. **(See the resource box, left, for links to government resources.)**

"The availability of a quick, easy, accurate HIV test will allow broader access to HIV diagnostic testing, help link those already infected to treatment and care services, and will allow those who are uninfected but at risk to avoid infection through prevention services," Janssen states.

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Check counseling skills with rapid HIV tests

Will your facility soon be implementing the OraQuick Rapid HIV-1 Antibody Test? If so, there are several resources to help you get up to speed in offering this new service.

The Atlanta-based Centers for Disease Control and Prevention (CDC) recently has released revised guidelines for HIV counseling and testing, which are available on its web site. **(See the resource box on p. 15.)** The guidelines include information about HIV testing and its importance, tips on specific counseling to help reduce HIV risks, and information about post-test counseling for persons tested with rapid HIV tests.

Make sure when you deliver the news of a reactive rapid HIV test result that the patient understands that the test result is preliminary and further testing must be done to confirm the result. Persons who have a negative rapid test but have had a recent risk exposure must be counseled to obtain another test at least three months after the possible exposure to account for the possibility of a false-negative test result.

If a patient has a negative rapid HIV test, you definitively can report that the test result is negative and that they are not infected, unless they have had a recent (within three months) known or possible exposure to HIV.

For patients who have reactive (preliminary positive) test results, further testing is required to confirm the result. In giving preliminary positive results, the CDC recommends that clinicians:

- **explain** the meaning of the reactive test result in simple terms, avoiding technical jargon;
- **emphasize** the importance of confirmatory testing and schedule a return visit for the confirmatory test results;
- **underscore** the importance of taking precautions to avoid the possibility of transmitting infection to others while awaiting results of confirmatory testing.[1]

How can you accomplish this communication? Try a simple message, such as, "Your preliminary test result is positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus."

A counseling protocol for providing prevention counseling during one visit for clients receiving rapid test results, as well as other related material, has been developed by Project Respect-2. **(See the resource box on p. 15.)** A multicenter trial, Project Respect-2 is working with rapid HIV testing in looking for ways to provide HIV testing and counseling that are more effective at reducing clients' risk of becoming infected with sexually transmitted infections than current methods.

Address both components

According to the CDC, HIV counseling must include two components: provision of information and prevention counseling. If you provide a rapid HIV test, give the patient information about the rapid test and obtain informed consent for testing. Also offer prevention counseling.

Be prepared to provide the same type of information with a rapid HIV test as you use with a standard enzyme immunoassay. Information can be provided in a face-to-face meeting, or in a pamphlet, brochure, or video. The information should include:

- highlights about the HIV test, its benefits, and its consequences;
- ways HIV is transmitted and how it can be prevented;
- the meaning of the test results in explicit, understandable language;
- directions on where to obtain further information and, if applicable, HIV prevention counseling;
- where to obtain other services including treatment, if applicable.[1]

Seize the moment

For patients with preliminary positive rapid HIV test results, remember that you will have two opportunities for prevention counseling: one on the day they have the rapid test, and one when they return for their confirmatory results. However, when your patients test negative with the rapid test, you will have only one test-associated opportunity to get across your prevention message.

When discussing prevention, keep in mind the following suggestions from the CDC:

- Keep the session focused on HIV risk reduction.
- Include an in-depth, personalized risk assessment.
- Acknowledge and provide support for positive steps already made.

• Clarify critical rather than general misconceptions about HIV risk.

• Negotiate a concrete, achievable behavior-change step that will reduce HIV risk.

• Seek flexibility in the counseling technique and process, avoiding a "one-size-fits-all" approach.[1]

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HPV vaccine research yields promising results

What if you could offer your patients a vaccine for protection against human papillomavirus (HPV), a sexually transmitted disease (STD) that can cause genital warts and cervical cancer? Just-published results from a randomized double-blind study indicates that an investigational vaccine developed by West Point, PA-based Merck & Co. reduced the incidence of human papillomavirus type 16 (HPV 16) infection in 100% of women who previously had not been infected with the STD.[1]

According to the Research Triangle Park, NC-based National HPV and Cervical Cancer Prevention Resource Center, there are more than 70 HPV types. About 30 of these types are sexually transmitted and cause genital HPV. HPV infections account for about one-third of all new STD infections; about 20 million people are thought to have an active HPV infection at any given time.[2]

The investigational vaccine studied in the published paper is a monovalent vaccine intended to prevent infection by HPV 16. Of the more than 30 types of HPV known to infect the human genitalia, HPV 16 is the most commonly linked with cancer since it is present in 50% of cervical cancers.[3]

The monovalent vaccine is just one component of Merck's vaccine investigation, says **Kelley Dougherty**, manager of Merck-Vaccine public affairs. The company is pursuing investigation of a multivalent vaccine looking at HPV 16, 18, 6, and 11, she reports.

Because cervical cancer involves multiple HPV types, it is important to have a vaccine that will provide coverage for more than one type, says **Laura Koutsky**, MSPH, PhD, professor of epidemiology at the University of Washington in Seattle and lead author of the published paper. By including HPV 16, found in 50% of invasive cervical cancers, and HPV 18, identified in about 20% of cancers, such a vaccine could prevent up to 70% of invasive cervical cancers, notes Koutsky. The vaccine also would target HPV 6 and 11, which are associated with genital warts.

Look at the research

In the double-blind study, researchers randomly assigned 2,392 young women ages 16 to 23 to receive three doses of placebo or HPV-16 virus-like-particle vaccine, given at day 0, month 2, and month 6. Genital samples to test for HPV-16 DNA were obtained at enrollment, one month after the third vaccination, and every six months thereafter. Of the women who received the vaccine, 99.7% had seroconversion, and none became infected with HPV-16 after a median follow-up of 17.4 months. The paper includes information from the first two years of the study; the researchers expect to follow the women for an additional two years.

A total of 41 women in the placebo group tested positive for HPV-16 infection during the study; no cases were recorded in the vaccine group. Nine cases of HPV-16-related cervical intraepithelial neoplasia occurred among women who received the placebo; no cases were recorded among women who received the vaccine.

The vaccine generally was well tolerated, and the incidences of adverse experiences were similar between treatment groups, the investigators report. There were no vaccine-related serious adverse experiences, and the overall incidence of nonserious adverse experiences were comparable between treatment groups. The most frequent adverse experiences reported by both women who

EXECUTIVE SUMMARY

Results from a randomized double-blind study indicates that an investigational vaccine developed by Merck & Co. reduced the incidence of human papillomavirus type 16 (HPV 16) infection in 100% of women who previously had not been infected.

- Scientists are examining a multivalent vaccine aimed at HPV 16, 18, 6, and 11.
- By including HPV 16, found in 50% of invasive cervical cancers, and HPV 18, identified in about 20% of cancers, such a vaccine could prevent up to 70% of invasive cervical cancers.

RESOURCES

- **The National HPV and Cervical Cancer Prevention Hotline** offers free information to the public about risk reduction, diagnosis and treatment of HPV and the prevention of cervical cancer, including the most up-to-date Food and Drug Administration-approved technologies. Trained health communication specialists are available to address questions related to transmission, prevention, and treatment of HPV. The hotline is open from noon to 7 p.m., EST, Monday through Friday. Telephone (919) 361-4848.
- **To access the e-mail service and HPV chat room offered by the National HPV and Cervical Cancer Prevention Resource Center**, go to the American Social Heath Association web site, www.ashastd.org; click on "Programs and Resource Centers," then "HPV Resource Center." At the center web page, click on either "HPVnet Email Account" or "HPV Chat Room."

received the vaccine or the placebo were injection site pain, headache, and injection site redness.

Women seek HPV info

Women are looking for more information on HPV, say officials with the National HPV and Cervical Cancer Prevention Resource Center. Its telephone hotline provides up-to-date information on the virus, risk reduction, diagnosis and treatment, as well as support for emotional issues surrounding HPV such as self-esteem and partner communication. The center launched an HPV Chat Room in March 2002 and has seen an average 200 users per month. Its HPV e-mail service responds to some 150 queries each month. **(See the resource box, above, for more information on these services.)**

HPV infection is a chronic condition, even when it is asymptomatic. No therapy has been shown to eradicate the virus. For treatment of genital warts caused by HPV, providers can choose from cryotherapy; application of podophyllin; application of trichloracetic acid; or surgical removal via scissors, shaving excision, or electrocautery. Other provider-administered treatments include laser surgery or intralesional interferon. Patient-administered prescription treatments include podofilox gel (Condylox, Oclassen Pharmaceuticals, a division of Watson Pharmaceuticals, Corona, CA) and imiquimod cream (Aldara, 3M Pharmaceuticals, St. Paul, MN). ***(Contraceptive Technology Update* reported on genital wart treatments in April 2002; see "Examine genital wart treatment options," p. 43.)**

The promise of an effective vaccine against multiple HPV types is exciting, but much research must be conducted before a vaccine reaches the marketplace, says Koutsky.

"These are very promising results, but the bottom line is that until a vaccine is fully tested and available, the best way to prevent cervical cancer is to participate in routine Pap screening," she states.

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Male contraception: Search is on for options

When women enter your family planning clinic, you have a wide array of contraceptive options to offer them. But when men ask about prevention methods, you have three choices: hand them condoms, advise abstinence, or counsel on vasectomy.

While 2002 saw the introduction of the contraceptive patch and vaginal ring for women, no contraceptive method emerged on the commercial marketplace for men. However, researchers report that investigation of male methods is enjoying a resurgence in interest, as hormonal approaches may have acquired the critical mass needed to make the transition from academic research to pharmaceutical development.[1]

To expedite development of new approaches to regulating fertility, the Bethesda-based National Institutes of Health has awarded a five-year, $9.5 million grant to the Seattle-based University of Washington to establish an interdisciplinary Male Contraception Research Center. The center will be part of the Cooperative Contraceptive Research

EXECUTIVE SUMMARY

Investigation of male contraceptive methods is enjoying a resurgence in interest.

- The National Institutes of Health has awarded a five-year, $9.5 million grant to the University of Washington to establish an interdisciplinary Male Contraception Research Center.
- Current research is focusing primarily on suppressing the production of sperm, by hormonal or nonhormonal means, or seeking to inhibit the fertilizing ability of sperm.

Centers Program, funded by the Contraception and Reproductive Health (CRH) Branch of the National Institute of Child Health and Human Development.

In addition, the CRH has issued a request for applications that are focused on novel approaches to male fertility regulation, and it has issued a request for proposal for clinical trial expertise in male contraception, says **Diana Blithe**, PhD, CRH scientific officer.

Defining the challenge

Why has it been so difficult to develop a viable male contraceptive? Consider the challenging physiological task of controlling the male reproductive system. While a woman produces one egg a month, a man produces hundreds of millions of sperm each day. Women are fertile only until menopause; men continue to produce sperm throughout their adult lives.[2]

Current research approaches in male contraception primarily are focusing on two mechanisms of action. One approach is aimed at suppressing the production of sperm, by hormonal or nonhormonal means, while the second avenue seeks to inhibit the fertilizing ability of sperm.[2]

Researchers have looked at administering doses of testosterone to achieve blood concentrations that are significantly higher than normal. This causes the male pituitary gland to slow the release of two hormones — follicle stimulating hormone (FSH) and luteinizing hormone (LH) — that produce the signals necessary for sperm development. FSH and LH act in a feedback loop to maintain normal concentrations of testosterone.[3]

Scientists also have looked at progestins to block testosterone production in the testes, which hinders sperm formation. Since this approach results in a drop in testosterone concentrations in the blood, researchers have administered low doses of testosterone in conjunction with the progestins.[3]

Results of two recent investigations indicate such approaches may be effective. One study, which looked at the use of testosterone decanoate injections and etonogestrel implants, suggests that spermatogenic suppression is achieved.[4] In the other study, investigators compared levonorgestrel implants and testosterone transdermal patch to testosterone patch alone on the suppression of spermatogenesis.[5] The scientists expanded their research to include use of a combination of oral levonorgestrel and testosterone patch, as well as use of levonorgestrel implants and testosterone enanthate injection. Results indicate that the implant/injection option was the most efficient in suppressing spermatogenesis to a level acceptable for contraceptive efficacy.[5]

New androgen eyed

The New York City-based Population Council is examining several research options in male contraception using its trademarked synthetic androgen, MENT (7 alpha-methyl-19-nortestosterone). While the synthetic steroid resembles testosterone, MENT does not enlarge the prostate, a drawback that occurs when testosterone is given exogenously. The Population Council is researching a MENT implant, transdermal gel, and patch formulation for contraception purposes.

Dose-ranging studies are under way in Germany, Chile, and the United States, using MENT alone and MENT associated with other agents to achieve a complete suppression of sperm production in male volunteers, states **Regine Sitruk-Ware**, MD, the council's executive director of contraceptive development. When the appropriate dose is determined, researchers will begin a study with couples volunteering to test the method for contraception. This step will not be possible before scientists are certain of achieving 100% suppression of sperm production, she notes.

A large-scale contraceptive efficacy and safety study would not start before mid-2004; it would include 300 couples followed for one year, and it also would document recovery of fertility in a further year of follow-up, says Sitruk-Ware.

"If the results are successful, we would then have to document efficacy and safety in 1,200 couples followed over one year of therapy," she states. "Given these requirements, the method

would be approved and available for general use most likely in year 2008 or 2009."

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Abortion rates continue to drop in U.S. women

EXECUTIVE SUMMARY

U.S. abortion rates continue to drop, but not all groups are seeing a decline. Rates have increased among those who are economically disadvantaged, according to data from a national survey.

- Declines in abortion rates were particularly steep among teens, especially among those ages 15-17; the rate for this age group dropped by 39%.
- Abortion rates and birth rates for teens have been falling since the early 1990s, which indicates that fewer teens are becoming pregnant; however, the proportion of adolescent pregnancies ending in abortion remained stable from 1994 to 2000.
- Despite the declines, U.S. teens have higher pregnancy rates, birthrates, and abortion rates than adolescents in other developed countries.

While U.S. abortion rates are dropping, particularly among teens, the decline is not equally shared among all women. Rates have increased among those who are economically disadvantaged, according to just-published research from the New York City-based Alan Guttmacher Institute (AGI).[1]

Declines in abortion rates were particularly steep among teens, especially among those ages 15-17, the data reflect. The rate for this age group fell to 15 abortions per 1,000 women in 2000 from 24 abortions per 1,000 women in 1994, a decline of 39%.

Both abortion rates and birth rates for teens have been dropping since the early 1990s, respectively, which indicates that fewer teens are becoming pregnant; however, the proportion of adolescent pregnancies ending in abortion remained stable from 1994 to 2000.[1] Despite the declines, U.S. teenagers have higher pregnancy rates, birthrates, and abortion rates than adolescents in other developed countries.[2]

The drop in adolescent abortion rates is not a recent phenomenon; the decrease in adolescent abortion rates started in the late 1980s, says **Rachel Jones**, PhD, senior research associate at the institute. The decline is not due to teens having more babies; the proportion of teen pregnancies ending in abortion remained at 33% in the current analysis, the same ratio found in 1994.

The lack of change demonstrates that teens aren't having fewer abortions because they are having more babies; rather, teens are having fewer pregnancies, says Jones.

"We have done good work as a nation — teens are increasingly making better decisions about their future — but we still have a long way to go," says **Bill Albert**, director of communications and publications for the Washington, DC-based National Campaign to Prevent Teen Pregnancy. The organization's goal is to reduce the U.S. teen pregnancy rate by one-third between 1996 and 2005. "That's one of our primary rallying cries: Not to get complacent about this issue."

Better methods, less sex

What is behind the decrease in teen pregnancy rates? Teens are making better choices about sex, whether they are choosing to abstain or to use contraception consistently and correctly, says Albert.

An AGI analysis examining the reasons for the decline in rates between 1988 and 1995 found that three-quarters of the decrease was due to improved contraceptive use, while one-quarter was due to delayed sexual activity.[3]

To see if the 75/25 ratio still is in place, AGI researchers plan to examine upcoming data from the upcoming National Survey of Family Growth (NSFG), a national data set from the Hyattsville, MD-based National Center for Health Statistics. For the first time, the 2002 NSFG will include information from men and women, with some 12,000 men

and women ages 15-44 polled on such issues as contraceptive use, infertility, and parenting. Look for the first statistical reports from the survey to appear in early 2004, according to the national center.

Overall rates drop

The overall abortion rate in the United States decreased by 11% between 1994 and 2000, falling from 24 to 21 abortions each year per 1,000 women ages 15-44, according to an AGI analysis of a survey of more than 10,000 women obtaining abortions in 2000-2001.

While abortion rates have declined for most women, they have increased among the economically disadvantaged, according to the AGI analysis. According to the researchers, the findings indicate these women have high pregnancy rates, as well as a greater likelihood than women with higher incomes of ending a pregnancy in abortion.

What are the reasons behind this increase? Jones points to three possible factors, which AGI researchers hope to examine in further studies:

• Changes in welfare policies that occurred between 1994 and 2000 may have made it less feasible for economically disadvantaged women to carry unintended pregnancies to term.

• The decline in Medicaid access due to welfare reform may have resulted in decreased access to contraceptives and contraceptive services. While access to Medicaid for women was decreased, there was no substantial increase in Title X funding, which provides low-cost family planning services, notes Jones.

• The improved employment and educational opportunities seen in the 1990s may have made it less feasible for poor women to carry a pregnancy or an unintended pregnancy to term.

"Women may have felt that having a baby at this time in their life would have prevented them from taking advantage of employment and educational opportunities," says Jones.

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More generic OC options on the way

Get set to add more generic oral contraceptives (OCs) to your list of available birth control options as Corona, CA-based Watson Pharmaceuticals is rolling out its brand equivalents of Ortho-Cyclen and Ortho-Novum 7/7/7, two popular pills originally developed by Raritan, NJ-based Ortho-McNeil Pharmaceutical.

The two Watson OCs, MonoNessa and Necon 7/7/7, were scheduled for product launch at *Contraceptive Technology Update's* press time, reports **Patty Eisenhaur**, the company's director of investor relations. The company entered into a supply arrangement in October 2002 with OMJ Pharmaceutical, an affiliate of Ortho-McNeil Pharmaceutical, for a portfolio of oral contraceptives.

Necon 7/7/7, like Ortho-Novum 7/7/7, contains 35 mcg of ethinyl estradiol and a phasic (0.5 mg, 0.75 mg, and 1 mcg) dose of the progestin norethindrone. MonoNessa, like its brand equivalent Ortho-Cyclen, is formulated with 35 mcg of ethinyl estradiol and 0.25 mg of the progestin norgestimate. Barr Laboratories of Pomona, NY, also offers brand-equivalent options of the two Ortho-McNeil drugs: Nortrel 7/7/7 and Sprintec. **(*CTU* reported on Barr Labs' additions in its December 2002 article, "Pill options expand with new, generic OCs," p. 140.)**

As brand equivalents, the two Watson Pharmaceuticals pills follow in the stead of two popular OCs: Ortho-Novum 7/7/7 has been a longstanding phasic pill choice, and Ortho-Cyclen is consistently in the top three choices of birth control pill options in *CTU's* annual Contraception Survey. Ortho-Cyclen ranked third in the 2002 survey in formulary and nonformulary choices for 21-year-old nonsmokers, following Ortho Tri-Cyclen, another phasic 35-mcg pill from Ortho-McNeil, and Alesse, a 20-mcg monophasic pill from Wyeth-Ayerst Laboratories of Philadelphia. **(See the *CTU* article, "Pill still is popular family planning choice," in the November 2002 issue, p. 124.)**

A generic 'acne pill'?

Family planning providers may see a generic version of Ortho Tri-Cyclen later this year. Watson Pharmaceuticals and Barr Laboratories have announced plans to launch their versions of the popular pill, respectively tradenamed TriNessa

EXECUTIVE SUMMARY

New generic oral contraceptive (OC) choices are coming from Watson Pharmaceuticals. The company is introducing brand equivalents of Ortho-Cyclen and Ortho-Novum 7/7/7, two pills originally developed by Ortho-McNeil Pharmaceutical.

- A generic version of Ortho-McNeil's Ortho Tri-Cyclen may be available later this year, as Watson Pharmaceuticals and Barr Laboratories have announced plans for brand-equivalent products.
- The timing is dependent on whether Ortho-McNeil receives an additional six months' exclusivity on the drug.

and Tri-Sprintec. Availability hinges on whether Ortho-McNeil receives an additional six months' exclusivity on its product following the scheduled September 2003 patent expiration.

Since Ortho Tri-Cyclen received an indication for the treatment of mild to moderate acne from the Food and Drug Administration (FDA) in January 1997, it has become the nation's leading prescribed birth control pill.[1] **(See the March 1997 *CTU* article, "Ortho Tri-Cyclen first low-dose OC to be indicated for noncontraceptive use," p. 25.)** Thanks to an aggressive print and media advertising campaign, women often come into providers' offices requesting prescriptions for "the acne pill."

Kerry Raghib, CNM, MSN, a nurse-midwife at Trinity Medical Center, Medical Arts Clinic in Minot, ND, says generic OCs are used at her facility, with Watson Pharmaceuticals' Necon line being the most common selections. When a generic version of Ortho Tri-Cyclen becomes available, she says it will be offered at her clinic.

Are generic OCs available at your facility? For many family planning clinics, the discount pricing offered through bulk or nonprofit purchasing programs makes branded products the most cost-effective choice.

Michele Van Vranken, MD, medical director of the Annex Teen Clinic and West Suburban Teen Clinic in Minneapolis, says generic OCs are not used at any of her facilities.

"At two of the clinics, we use Ortho-Novum, Ortho-Cyclen, and Ortho Tri-Cyclen, but get a significant discount from Ortho as nonprofit entities," she states." We would consider using generics, though pricing will be a factor, and I don't know that the generics will be less than the discount currently offered."

Are generic oral contraceptives as effective as brand-name pills? First, it is important to understand what constitutes a therapeutic equivalent drug. For two products to be considered pharmaceutically equivalent, they must contain the same active ingredients and be identical in strength, dosage form, and route of administration. Bioequivalence is achieved if the generic product demonstrates no substantial difference in rate or extent of absorption when compared to the reference drug.[2] Multisource drug products listed under the same heading — identical active ingredients, dosage form, and route of administration — and having the same strength generally will be coded AB if a study is submitted demonstrating bioequivalence. All the bioequivalent hormonal contraceptives on the market today are AB-rated.[3]

FDA approval guidelines for generic products require one small crossover study to demonstrate bioequivalence.[4] The FDA considers two products bioequivalent if the extent of absorption for the generic is 80%-125% of that of the brand-name drug.[4] No data are available for clinicians to review the occurrence of side effects, breakthrough bleeding, or unintended pregnancy between generic and brand-name OCs; the FDA does not require these studies for approval of generic drugs.[4] (The Washington, DC-based Association of Reproductive Health Professionals addresses the use of generic OCs in the August 2001 electronic edition of its publication, *Clinical Proceedings;* to review, go to www.arhp.org and click on "Health Care Providers," "Online Publications," "Clinical Proceedings," and "Understanding Low-Dose Oral Contraceptives.")

For patients who pay for prescriptions at retail pharmacies, however, the reduced price of generic products can be attractive. Insurance prescription plans may not cover contraceptives, so women may be looking for cost savings when it comes to directly paying for birth control.

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ASK THE EXPERTS

Answers to EC protocol, DMPA impact on lipids

Puzzled about protocols for dispensing emergency contraception (EC) to male partners? Wondering about the impact of depot medroxyprogesterone acetate (DMPA, Depo-Provera, Pharmacia Corp, Peapack, NJ) on lipid levels?

The following members of *Contraceptive Technology Update's* Editorial Advisory Board address these issues: **Linda Dominguez**, RNC, NP, assistant medical director of the Albuquerque-based Planned Parenthood of New Mexico; **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center / Jacksonville; **Michael Rosenberg**, MD, MPH, clinical professor of obstetrics and gynecology and adjunct professor of epidemiology at the University of North Carolina at Chapel Hill and president of Health Decisions, a private research firm specializing in reproductive health; and **Felicia Stewart**, MD, adjunct professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California San Francisco and co-director of the Center for Reproductive Health Research & Policy.

Question: I'm a public health nurse working in a family planning clinic. Within our county, we have three outlying clinics within 30-60 minutes of the metropolitan center. Those clinics are staffed only one to three days per week. On several occasions, we have had young men present in the clinics requesting EC for their girlfriends who are unwilling to come in for fear of being seen by an acquaintance in the small community. We are attempting to gather information about the possibility of dispensing EC to male partners for immediate use. Can you provide any precedence or protocols that would address this?

Dominguez: The one informal protocol that comes to mind that is similar is the provision of prescription or dispensing extra medication for treatment of sexually transmitted diseases (STDs) for recent contact partners. This has been a sanctioned practice documented in the CDC Guidelines for the Treatment of Sexually Transmitted Diseases.

Another solution would be a telephone intake by staff with the woman and then provision of prescription to local pharmacy. Your public health clinic would need to work up a procedure / protocol. Paperwork would have to be generated to establish a relationship with the patient to satisfy the need for a provider / patient interaction for prescribing regulations. Also the public health department would want to capture this patient contact for their numbers.

Rosenberg: I don't know of any protocols, but the basic message around EC use is that it is remarkably safe and needs to be used on a timely basis. Partner treatment is an accepted component of STD treatment, and I believe that EC use should similarly be encouraged.

Stewart: Maybe the clinic could speak to the woman by telephone, and then the partner could pick it up? That way, the prescription is for the woman, and the clinician has a chance to gather confidential info directly from her, but the convenience issue is dealt with.

Question: What effect does Depo Provera have on cholesterol? Has it been found to create any problems because of the lowered estrogen effects in women who take Depo Provera for years?

Kaunitz: Use of DMPA contraception lowers HDL levels and raises LDL levels. In contrast to use of oral contraceptives, triglycerides do not rise with use of DMPA. The clinical implications, if any, of these findings are unknown. Regarding lower estrogen production by the ovaries during use of DMPA: Bone mineral density declines during use of DMPA, then rises back toward baseline after use of injectable contraception. This phenomenon appears similar to what happens with bone density during lactation (another state associated with lower estrogen levels). Long-term implications, including osteoporosis or fractures, have not been demonstrated to result from use of DMPA birth control. ■

COMING IN FUTURE MONTHS

- EC use linked to decline in abortion rates
- Update on contraceptive injectables
- Tips on common problems with the Pill
- Barrier methods: New approaches in the works
- Teens: Talking points on pregnancy prevention

CE/CME Questions

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

- Name the type of specimen tested with the OraQuick Rapid HIV-1 Antibody Test. **(See "Rapid HIV testing method approved — prepare now to apply new strategies" in this issue.)**
- State two Food and Drug Administration-approved drugs for patient-administered prescription treatment of genital warts. **(See "HPV vaccine research yields promising results.")**
- Identify the available methods of male contraception **(See "Male contraception: Search is on for options.")**
- Cite the number of women with herpes simplex virus 2 infection **(See "Herpes vaccine research may hold key to stemming STD.")**

5. What type of specimen is tested with the OraQuick Rapid HIV-1 Antibody Test?

A. Serum or plasma
B. Fingerstick whole blood
C. Oral fluid
D. Serum

6. Which of the following is <u>not</u> a currently available method of male contraception?

A. Condoms
B. Abstinence
C. Vasectomy
D. Combination of levonorgestrel implants and testosterone enanthate injection

7. What are two Food and Drug Administration-approved drugs for patient-administered prescription treatment of genital warts?

A. Podofilox gel and imiquimod cream
B. Podofilox gel and permethrin cream
C. Metronidazole and imiquimod cream
D. Terconazole and imiquimod cream

8. How many women are estimated to have herpes simplex virus 2 (HSV-2)?

A. One in four
B. One in three
C. One in 10
D. One in five

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AMERICAN HEALTH CONSULTANTS

Contraceptive Technology Reports

A supplement to *Contraceptive Technology Update* **February 2003, BB #S03154**

Introduction

Editor's note: *This article discusses a use of quinacrine that has not been approved by the Food and Drug Administration.*

Sterilization in the Office: The Concept Now is a Reality

Author: **Susan A. Ballagh,** MD, FACOG, Assistant Professor of Obstetrics and Gynecology, CONRAD/Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk.

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Despite an increasing number of birth control methods, surgical sterilization is the most common form of birth control for women 15-44 years of age in the United States. Eleven million women rely on sterilization for contraception, and an estimated 500,000 men are sterilized annually in the United States.[1] Sterilization is used much more commonly in the United States than in Europe, in part because U.S. medical insurance has covered all or part of the sterilization procedure but has not covered reversible contraception until recently. The 1965 National Fertility Study showed approximately equal numbers of men and women receiving sterilization procedures.[2] Today, more than twice as many women as men are sterilized annually.[2] The convenience of an office procedure has been afforded only to men, until the recent approval of the first office procedure for female sterilization.

The zenith of tubal sterilization for women was in 1977 when more than 700,000 women underwent the procedure. The peak coincided with exaggerated concern about the safety of long-term oral contraceptive use during the 1970s.[3] Today about half of the 600,000 tubal sterilizations performed annually are done at cesarean section or immediately postpartum.[3] The vast majority of the remaining procedures are interval tubal sterilizations performed with a laparoscope under general anesthesia in an outpatient setting. More women depend on sterilization as their contraceptive method as they get older: 5% of 20- to 24-year-olds compared to nearly half of 40- to 44-year-olds count on female sterilization.[3] Women of color choose sterilization more often: 25% of African-American, 21% of Latin-American, and 16% of Caucasian women use tubal ligation as their birth control method.[3]

Reversible methods with efficacy equivalent to sterilization, such as intrauterine contraception, are rarely chosen in the United States. Fear generated by the flawed Dalkon Shield, manufactured in the 1970s by AH Robins in Richmond, VA, has generalized to all intrauterine devices. Large initial investment cost coupled with spotty insurance reimbursement has impeded acceptance of these devices.[4] Contraceptive implants provide similar pregnancy prevention, but are no longer marketed in the United States. Injections have similar efficacy when used properly, but the discontinuation rate is high because women must physically come to an appointment to continue the method. Women and many physicians are unaware that these reversible methods are just as effective as sterilization. While somewhat less convenient, the reversible methods clearly are preferred in situations in which women are likely to regret their sterilization decision, which include women younger than 30 years of age, women sterilized within one year of the birth of their last child, and women who are unmarried at the time of the sterilization.[5]

History of Transcervical Sterilization

Sterilization by minilaparotomy has been practiced since the early 1900s. Techniques for sterilization also were done by colpotomy. With the advent of fiberoptic technology, endoscopic methods to apply cautery, clips, or bands to the tubes for occlusion in an outpatient setting were developed. Both the vaginal and abdominal routes were employed to provide tubal blockage, but some form of anesthesia was required, and infections were problematic. A means to perform female sterilization in the office proved elusive. Several transcervical approaches to sterilization were explored in the 1970s — chemical agents and physical barriers — but none has reached general use until now.

Chemical Methods of Transcervical Tubal Blockage

The most studied transcervical sclerosing agent is quinacrine, a drug first used more than 70 years ago to prevent and cure malaria. An intrauterine device (IUD) inserter was modified to introduce quinacrine pellets into the uterine fundus to chemically block the fallopian tubes and prevent pregnancy. The Food and Drug Administration (FDA) has not approved this procedure. Two rodent carcinogenicity studies have been requested and are in progress. The pellets are estimated to cost less than $20 and would provide an inexpensive approach to tubal sterilization.

Safety. Quinacrine has a long history of human use. More than 3 million American soldiers took quinacrine orally while serving in the South Pacific to prevent malaria with no serious long-term side effects.[6] No evidence of carcinogenesis was noted among nearly 1,500 women sterilized by Jaime Zipper, MD, in Chile. He followed these women over 13,000 person-years and observed 25 cancer cases, which is equivalent to the expected rate of 22.[7] In a Vietnamese trial of nearly 32,000 women, no deaths were reported. Only one woman required hysterectomy for infection/hemorrhage that followed the third pellet insertion. Two women were dilated to relieve hematometra due to cervical stenosis.[8] Accidental perforation of the uterus depositing quinacrine intraperitoneally resulted in marked abdominal pain, but it did not cause bowel obstruction or require surgery.[9] Overall, quinacrine pellets have been placed into the uterus in more than 100,000 women, with no deaths attributed to the procedure.[10]

Mechanism of Action. Hysterectomy evaluation one month following quinacrine insertion demonstrated that nine of 17 available tubes had obliteration of the lumen or absence of the epithelium. The other eight tubes showed mild inflammation. No intrauterine adhesions were detected. The one case of intraperitoneal adhesion between the fundus and the omentum was assessed as unrelated to the pellets by the investigator.[11]

Efficacy. The efficacy of the pellets was improved by Indian investigators who coupled the insertion of 242 mg of quinacrine (seven pellets) with a 50-mg intrauterine dose of diclofenac and an injection of 150 mg of depo-medroxyprogesterone acetate. A repeat insertion of quinacrine and diclofenac was performed one month later. One hundred and thirty-four women were followed for a minimum of one year and a mean of 3.5 years.[12] No pregnancies were reported. Zipper, by contrast, reported 3.1 failures per 100 women at one year with three pellet insertions.[13] The deposition of the pellets high in the fundus results in superior pregnancy prevention as reported by Biaragi and co-workers.[14] For all ages, an interim analysis of the five-year experience in Vietnamese women showed an overall success rate with two insertions of 87%. Only 6.8% of the women older than age 35 conceived while relying on the pellets during the five-year follow-up.[10]

Family Health International in Research Triangle Park, NC, is studying the use of macrolide antibiotics such as erythromycin for nonsurgical female sterilization. Tetracycline is another antibiotic that has been studied. Other chemical methods previously attempted for tubal blockade include papavarine, phenol-mucilage, and methylcyanoacrylate.[15] The latter is a tissue adhesive that hardens

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through polymerization when hydrated. An initial occlusive plug is formed that degrades over several weeks and releases a sclerosing molecule as a by-product. The product was introduced with an intrauterine balloon device to force a measured dose of product into the tubes. Following two instillations, less than or equal to 90% bilateral tubal occlusion was noted, so the method was abandoned. An iodine-releasing polymer is being investigated as a possible alternative. Another compound that has been tested in rabbits is ethylene vinyl alcohol copolymer.[16]

Physical Methods of Transcervical Tubal Blockage

The concept of providing sterilization through the cervix has captivated researchers since fiberoptic technology allowed visualization of the tubal ostia. A great deal of research in the 1970s resulted in several devices designed to be placed into the tube. Others attempted sterilization by destroying tubes with heat, laser,[17] cautery, or cryosurgery with variable success.[15]

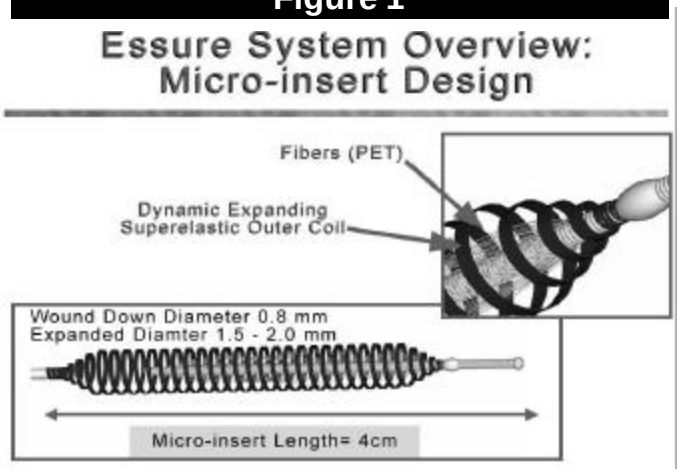
Steptoe[18] reported on a silicon rod inserted into the oviduct in 14 women. Other hysteroscopically applied plugs included the P block plug[19] that swelled with hydration to occlude the tube, the Hamou tubal plug — a plastic thread anchored in the interstitial portion of the tube.[15] The drawbacks of the plug systems included the tendency for the plug to migrate or fracture[20] and limited success in placing the devices.

Ovabloc. Another method injected liquid silicone hysteroscopically into the tubal ostia. Once hydrated, the material cured quickly forming a cast of the fallopian tube.[21] Reed reported that 1,400 (78%) of 1,800 procedures were considered to be successful. Uterine perforation occurred five times, and 11 patients had spontaneous separation or expulsion of the plugs at 3-24 months.[22] Of the 438 women sterilized at his center, 309 (71%) had proper plugs form bilaterally by follow-up X-ray. Ninety-one women were sterilized a second time, and 45 (50%) had bilateral X-ray occlusion after the second attempt. Three of the initial 309 women became pregnant during 8,600 months of follow-up,[22] equivalent to 0.4 pregnancies per 100 woman-years of use. The pregnancies were intrauterine and occurred between five and 22 months after placement. In another report, six pregnancies were noted in 275 women, for a pregnancy rate of 2.3 per 100 woman-years.[23] Designed to be reversible, no pregnancies were reported followed removal or spontaneous expulsion. Any hope for the product was dashed when Dow Corning Corp. discontinued production of medical-grade Silastic in the late 1980s.

New FDA-Approved Device: Essure

A new approach to transcervical sterilization blocks the tube by encouraging local tissue in growth with polyester (PET) fibers. To anchor the polyester in place, an attached outer super-coiled spring is released that molds to the shape of the interstitial (uterine) portion of the tube. The FDA approved this device called Essure in November 2002 for tubal sterilization. It is made of an alloy outer coil, a stainless steel inner coil, and the PET fiber core. The expandable coils provide stability, while the polyester encourages tissue in growth resulting in occlusion. The plug induced in the tube is made of the woman's own tissue reaction. **(See Figure 1, above.)** The device costs about $950. It is designed for interval sterilization and is not to be used at cesarean section or immediately postpartum.

Figure 1



Source: Association of Reproductive Health Professionals. Transcervical methods in the U.S. pipeline. *Clinical Proceedings* 2002; May:9.

Procedure. The Essure device is designed for office-based application with a special inserter that comes prepackaged with the system. Hysteroscopy using normal saline is best performed during the follicular phase closely following menses. This reduces the chance of inadvertent luteal pregnancy and provides the best environment for device placement. Thickened endometrium seen in the luteal phase may obscure the tubal ostia. The device is designed to pass through a hysteroscope operating channel with a minimum inner diameter of 5 French. Olympus, Stortz, and Wolfe manufacture scopes with inflow and outflow capability of approximately less than or equal to 5.5 mm outer diameter that have been used for this purpose. A 30-degree device improves the lateral view of the tubal ostia. Insertion of these two devices may require more than one operation. It requires a physician trained to insert Essure.

Nonsteroidal premedication is strongly recommended not only for patient comfort, but to reduce the chance of tubal spasm. A paracervical block, other local anesthesia, or oral or injected narcotic may be used as adjuncts. In the Pivotal Trial (described further in this article), 41% of women used intravenous sedation, and 7% did not use any anesthesia except the required paracervical block. In our office and several others, no IV sedation was available. Some women do better watching the procedure on a monitor to distract them from pain and reduce their trepidation. Dim lighting and

music via headphones is soothing for others. All the women in our clinic could correctly identify the side being occluded during the procedure.

Once prepped for diagnostic office hysteroscopy, the scope often can be advanced into the cavity with minimal cervical dilation under direct guidance. It is recommended to visualize both ostia and then guide the first micro-insert into the least accessible ostium. An assistant opens the device, preloaded into its inserter, using sterile technique and assists in introducing the apparatus into the operating channel. The device is passed into the tube under direct visualization of the ostium up to a black marker. The outer delivery catheter is then withdrawn, while taking care to maintain the position of the coil itself. Minor adjustments of the position of the coil still can be made in most cases until the device is released. Pressing a button on the handle of the inserter releases the coil and allows it to expand. The guidewire is gently twisted off the device and then removed. The catheter system is similar to that used for cardiovascular stent placement.

Essure is operated with one hand so that the surgeon can stabilize the hysteroscope with the other. A 6-10 mm portion of the coil should be visible in the uterine cavity after the device is placed. The guidewire and outer delivery catheter are removed from the operating channel, and the second device is loaded into the hysteroscope. Then the other ostium is located, and the placement procedure is repeated on the contralateral side to complete the sterilization.

Mechanism of Action. To demonstrate the occlusive tissue reaction, 49 women had the device placed several weeks to several months prior to hysterectomy.[24] At the subsequent hysterectomy, the fallopian tube and uterus were removed in one block. Pathology showed a fibrotic and inflammatory response localized to the region of the tube containing the device. The tissue reaction was confined to the mucosa and muscularis layers. The tubal serosa appeared normal. Fallopian tube architecture began to normalize just 5 mm from the end of the device. Occlusion appeared complete.[25]

Pivotal Trial. The clinical trial for device registration was conducted in Australia, Europe, and the United States.[26] Six hundred and fifty women met initial inclusion and exclusion criteria for the study and provided informed consent. Women were not considered if they had unexplained pelvic pain, fibroids, or other known uterine or tubal abnormalities. Ninety-two later voluntarily withdrew from the study, 24 failed screening primarily due to an abnormal pap smear or irregular menses, and five became pregnant. Eleven women older than 33 years of age had been consented but did not get the procedure because enrollment closed for their age group.

A total of 518 women underwent hysteroscopy, and 507 (98%) of them had visible tubal ostia. Of these women, 446 had successful bilateral device placement during the first procedure. Eighteen additional women had successful completion of the procedure at a second attempt. Two women were found to have a unicornuate uterus, and 10 had unilateral placement only. Overall, 466 women (92%) had proper device placement. Four women had a perforation, and in three women, the device lay in an unsatisfactory location. No complication required major surgery. The only hospitalization that followed the procedure was due to a reaction to pain medication. By protocol, women were to use another form of birth control until a hysterosalpingogram confirmed tubal blockage at three months. During that time, 14 women (3.0%) experienced an expulsion of one or both devices. Procedures with more than 16 mm of coil extending into the uterine cavity had a higher rate of expulsion. Nine of these women had Essure reinserted successfully. In the Pivotal Trial, 92% of women returned to work in one day; most resumed normal activities the same day as the procedure.

Efficacy. 453 women (89% of the initial intention to treat population) relied on Essure for contraception for one year after documentation at three months (428) or later (25) that the device prevented dye spillage into the abdominal cavity. No pregnancies were noted during the first year of follow-up. At two years, the effectiveness rate quoted by the company is 99.8%.[27] This rate is at least as good for the first two years as other interval sterilization methods. Five-year data will be required to properly compare results to data on other sterilization methods from the U.S. Collaborative Review of Sterilization (CREST).[28] In a manner similar to vasectomy, the required hysterosalpingogram at three months provides a functional test of tubal occlusion that verifies the success of the procedure. Compared to other tubal sterilization techniques, the hysterosalpingogram at three months and the necessity of using an alternative contraceptive until the hysterosalpingogram results are completed add to the cost and complexity of the Essure technique. Compared to vasectomy procedures for men, the functional test to determine the success of the Essure procedure is more complex and more expensive.

There were four luteal phase pregnancies noted during the trial, despite negative urine pregnancy tests on the day of the procedure. These pregnancies were terminated surgically (2), medically (1), and spontaneously without device disruption.

Comfort. The protocol limited the time for hysteroscopy to 30 minutes. The average operating time was 13 minutes, with a median of 10 minutes. The total procedure time was 36 minutes, with a median time of 32 minutes. Most surgeons reduced their time of procedure significantly after the first five procedures. Additional decrease in operating time was noted with more experience but was not statistically significant. Eighty-four percent of women received some nonsteroidal medication before the procedure. Fifty-two percent received local anesthesia, while 41% received intravenous sedation or narcotic analgesia. Only 0.2% of subjects had general anesthesia, and 7% chose to forego analgesia altogether. Three-quarters of the women reported the average

pain of the procedure to be mild or none. Only 1% said that the average pain was severe. More than 95% of women at the end of the first week and more than 99% of women at the end of one year said that they felt good, very good, or excellent. More than 95% would recommend it to a friend.

Adverse Events. Of the 518 women with hysteroscopy, three had a vasovagal reaction, three had vomiting after the procedure, two had hypervolemia, two had a portion of the device detach due to improper surgical technique, and one had excessive vaginal bleeding. Four perforations were noted: In two, women had a proximally occluded tube, and in two, the ostia were poorly identified. There were six minor complications. In the week following the procedure, 94% of women had bleeding or spotting that lasted less than four days for most women. More than 70% of employed women missed less than one additional day of work following the procedure. Virtually all women (> 95%) were back to work within three days. No major change in menstrual function was detected. Some increased spotting, infrequently requiring sanitary protection, was reported by trial participants, especially just prior to or just preceding the menses. This spotting lessened with time. During the first year of contraceptive use, other side effects possibly related to the product included back pain (9%), abdominal pain (3.8%), and dyspareunia (3.6%). All other events were noted in fewer than 3% of women. Only 448 of 518 women (86.5%) had successful device placement for sterilization at the time of the first procedure. This is a major disadvantage of transcervical sterilization via the Essure technique.

Warnings.[29] Unlike tubal interruption procedures where tubal segments may be reconnected with significant success, tissue in growth in the interstitial portion of the tube has not been shown to be surgically reversible. Given the high rates of regret following tubal sterilization in published studies, it would be wise to inform women considering having the Essure procedure done that reversal is more expensive and less successful than reversal of current tubal sterilization techniques.

Procedures to reverse this type of sterilization will require tubal reimplantation into the uterus with a much lower success rate and a risk of uterine rupture during a subsequent pregnancy. While tubal ligation always should be performed with the intention that it be permanent, this procedure is ill advised for women with a high probability of regretting their decision in the future. The inserts can conduct energy to surrounding tissue, so energy application should be avoided near the inserts during procedures that use radio frequency energy such as endometrial ablation or surgical cautery.

The Essure device can provide permanent sterilization in the physician's office. Some physicians may feel more comfortable performing the procedure initially with IV sedation readily available, but a number of centers perform the Essure procedure in the office. It is highly effective without incision or general anesthesia. Women recover quickly. Similar to vasectomy, the procedure should not be used for contraception until a functional test, in this case the hysterosalpingogram (recommended at three months), demonstrates successful blockage of the tubes.

Adiana Procedure. Another device in development would use a two-step process. A catheter passed through a hysteroscope into the intramural portion of the fallopian tube would deliver low-level bipolar energy to remove surface epithelium. Following cautery, a permanent porous implant would be placed at the site of the lesion to encourage tissue in growth similar to the Essure process described above. It has been tested in early (Phase I) clinical trials and appears to be safe with little discomfort associated with it.[10]

Intratubal Ligation Device. A catheter in development would be inserted into the tube using hysteroscopic guidance or possibly blind placement. A balloon coated with adhesive would inflate to 4-5 mm and make contact with the mucosa. Once firmly attached, the balloon would deflate and retract, which allows a band to be placed around the folded knuckle of tube. The band would provide immediate occlusion, but it likely would lead to necrosis and scar formation providing permanent blockage. The device is being tested in animal tissue and excised human oviducts.

Reversible Tubal Occlusion Device. The device to be introduced through the hysteroscope would be made of a nickel-titanium to cause minimal tissue injury. The device would have a unique structure that would allow mechanical or electrical reversible closure of the fallopian tube.

Summary

After several decades of development, a new transcervical sterilization office procedure is available to women in the United States. Essure micro-inserts provide office sterilization that is safe, effective, and well tolerated without incisions or general anesthesia. Sclerosing agents and other devices are discussed briefly and suggest that additional options may become available within the next decade to give women other office-based choices for female sterilization.

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CME Objectives

After reading this issue, the CME participant will be able to:

- list the contraceptive method used by more couples in the United States than any other;
- identify the method(s) of contraception with efficacy equivalent to tubal ligation;
- identify women most likely to regret their decision to have permanent sterilization;
- identify the key advantages of transcervical sterilization;
- list the drawbacks of the Essure transcervical sterilization method.

CME Questions

Effective with this issue, Contraceptive Technology Reports *is changing its testing procedure. You will no longer need to return a Scantron answer sheet to earn credit for the activity. Please review the text, answer the following questions, check your answers against the key on the following page, and then review the materials again regarding any questions answered incorrectly. To receive credit for this activity, you must return the enclosed CME evaluation in the enclosed envelope.*

This testing procedure has proven to be an effective learning tool for adults. If you have any questions about the new testing method, please contact Customer Service at (800) 688-2421.

1. What method birth control used by more women in the United States than any other?
   A. oral contraceptives
   B. male sterilization
   C. female sterilization
   D. male or female condoms
   E. injectable or implantable hormonal methods

2. The method(s) of contraception with efficacy equivalent to tubal ligation include(s):
   A. intrauterine contraceptives, Lunelle monthly injections, and vasectomy.
   B. intrauterine contraceptives and vasectomy.
   C. Lunelle monthly injections and transdermal contraception.
   D. transdermal contraception or the vaginal ring.

3. Women most likely to regret their decision to have permanent sterilization:
   A. are younger than 30 years of age, have been pregnant within the past year, and unmarried.
   B. are younger than 30 years of age and unmarried.
   C. have been pregnant within the past year and have two or fewer children.
   D. have two or fewer children and are unmarried.

4. The key advantage(s) of transcervical sterilization include:
   A. use of local anesthesia, no incision, and office procedure.
   B. use of local anesthesia, and office procedure.
   C. no incision and easily reversible.
   D. easily reversible and office procedure.

5. The drawback(s) of the Essure transcervical sterilization method include:
   A. little time required off from work, difficulty removing the micro-inserts once placed, and slow reversal of the contraceptive effect.
   B. little time required off from work and slow reversal of the contraceptive effect.
   C. Difficulty removing the micro-inserts once placed and ability to conduct cautery or radio frequency energy.
   D. Ability to conduct cautery or radio frequency energy (only).

Answers: 1. C; 2. A; 3. A; 4. A; 5. C.

CME Participation

Physicians participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, please complete the evaluation form provided and return in the reply envelope that also is provided. A certificate will be mailed to you.

S·T·D QUARTERLY™

Herpes vaccine research may hold key to stemming STD

Researchers enrolling some 8,000 women in pivotal efficacy trial

You have just finished counseling a young woman who is frightened and confused after hearing she has contracted genital herpes. While you are able to offer her daily suppressive therapy to help reduce the frequency of outbreaks, you discuss the fact that there is no cure for this sexually transmitted disease (STD).

What if there were a vaccine available that would offer protection against the types of herpes simplex virus (HSV) that lead to genital herpes, HSV-2, and in some cases, HSV-1? Researchers may be closer to delivering such a vaccine, as a major pivotal efficacy trial of an experimental vaccine has just begun following the publication of Phase III trial results indicating that an experimental vaccine reduced the incidence of genital herpes by more than 70% in uninfected women.[1]

The pivotal trial eventually will enroll 7,550 women in at least 16 sites in the United States. It is the result of a partnership between the Bethesda-based National Institute of Allergy and Infectious Diseases (NIAID) and the vaccine's manufacturer, GlaxoSmithKline Biologicals, with headquarters in Rixensart, Belgium.

Finding thousands of HSV-negative women for the new trial will be a significant challenge, says **Pamela McInnes**, DDS, MSc, deputy director of NIAID's Division of Microbiology and Infectious Diseases.

"In the adult population as a whole, it is estimated that one in four women has HSV-2, and an estimated 66% of adults have HSV-1," she states. "Depending on the population being screened, we anticipate screening at least three women for every one determined to be both HSV-1- and HSV-2-negative."

The need for a vaccine is great: More than 1 million new cases of genital herpes are diagnosed in the United States each year. According to two national surveys between the 1970s and the 1990s, genital herpes increased fastest among white teens ages 12-19.[2] Herpes prevalence in that population was five times greater than the prevalence in the 1970s. Among young white adults ages 20-29, herpes prevalence increased twofold over that same time period.

While genital herpes infection often manifests

EXECUTIVE SUMMARY

A major pivotal efficacy trial of a vaccine for genital herpes has just begun. It follows the publication of Phase III trial results indicating that an experimental vaccine reduced the incidence of genital herpes by more than 70% in uninfected women.

- The need for a vaccine is great: More than 1 million new U.S. cases of genital herpes are diagnosed each year.
- While genital herpes infection often manifests itself in subtle symptoms, it can be a devastating illness in newborns.
- It also has been identified as a risk factor for the spread of HIV/AIDS in adults.

itself in subtle symptoms, it can be a devastating illness in newborns, and it also has been identified as a risk factor for the spread of HIV / AIDS in adults.

Examine new results

Results of the latest research stem from two trials of the vaccine, reported in the same paper.[1] The initial study analyzed the effects of the three-dose vaccine in a total of 268 women and 579 men free from infection with HSV-1 and HSV-2. In the second study, researchers looked at 710 women and 1,157 men who had not been infected with HSV-2. In both groups, the study subjects' regular sexual partners had a history of genital herpes. As in the first study, the recipients were injected with the vaccine followed by a second dose a month later and a third dose after six months.

Volunteers will be assigned randomly to receive the candidate vaccine or a vaccine against hepatitis A, which will allow all participants a chance to be protected from a disease.

In the first group of women tested, the vaccine proved 73% effective in protecting against genital herpes disease for 19 months, the duration of the study. In the second group, which was designed to focus on those not previously infected with HSV-2 alone, analysis showed that the vaccine was 74% effective in preventing genital herpes in women who had not been infected with HSV-1 or HSV-2.

Why was the vaccine more effective in women than in men? Researchers believe there may be two explanations, which may not be mutually exclusive, says **Lawrence Stanberry**, MD, PhD, chairman of the Department of Pediatrics at the University of Texas Medical Branch at Galveston (UTMB) and lead author of the paper.

The vaccine under research uses a genetically altered snippet of the HSV-2 virus called HSV-2 glycoprotein-D-subunit and a new type of adjuvant, a substance that causes a nonspecific immune response to boost the effectiveness of the vaccine. The adjuvant contains a combination of alum and 3-O-deacylated-monophosphoryl lipid A (3d-MPL), which Stanberry describes as a very potent substance in inducing T cell responses. Given that the vaccine elicited a better response in women, it may be possible that the adjuvant system just works better in women than in men, he says.

The other possible explanation for the vaccine's increased protection for women may lie in the way women and men get infected with genital herpes, he suggests. Women most likely get infected on a mucosal surface, he notes. When women are vaccinated, their bodies make immune responses that go to that mucosal surface. Men, on the other hand, probably get infected through breaks in the skin, and not on mucosal surfaces, Stanberry notes.

"When you think about the vaccines being at the portal of entry, it would require that the vaccine in a man produce immune responses that are just sort of sitting just under the skin waiting for the virus to gain entry," explains Stanberry. "So it could be that just because of the differences in the way men and women get infected, the vaccine works better in women, because it can prevent that first step."

Enrollment under way

The new vaccine trial is being conducted at multiple sites across the United States as a double-blind, randomized, controlled Phase III efficacy trial. The study will be coordinated by St. Louis (MO) University; other sites include Baylor College of Medicine, Houston; Children's Hospital, Cincinnati; Harborview Medical Center, Seattle; Harbor — University of California Los Angeles Medical Center, Torrance, CA; Indiana University, Indianapolis; Johns Hopkins University, Baltimore; Louisiana State University, New Orleans; Primary Physicians Research, Pittsburgh; University of Alabama, Birmingham; University of Colorado Health Sciences Center, Denver; University of Maryland, Baltimore; University of North Carolina, Chapel Hill; University of Rochester (NY); University of Utah Medical Center, Salt Lake City; and Westover Heights Clinic, Portland.

Volunteers will be assigned randomly to receive the candidate vaccine or a vaccine against hepatitis A, which will allow all participants a chance to be protected from disease. Volunteers will be vaccinated at the start of the trial and at one and six months after the first injection. The women will be followed for 20 months after the initial vaccination to determine whether the

candidate vaccine prevents HSV infection or disease. Women between the age of 18 and 30 who wish to be evaluated for possible inclusion in the trial should visit the NIAID's web site at www.niaid. nih.gov/dmid/stds/herpevac/.

While it is too early to predict the outcome of the new trial, Stanberry says he is encouraged by the results of the research that has been completed in looking toward an effective weapon against the STD.

"These are very exciting findings," he notes. "These new studies suggest that a comprehensive campaign to vaccinate girls and women not infected with either type of herpes simplex virus could significantly reduce the spread of the herpes epidemic in the general population."

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Syphilis rate rises for first time since 1990

EXECUTIVE SUMMARY

Overall rates of primary and secondary syphilis have increased slightly for the first time in more than a decade, according to the Centers for Disease Control and Prevention (CDC).

- The CDC initiated efforts in 1998 to eliminate syphilis from the United States, with elimination defined as the absence of sustained transmission.
- The increase in rates is attributed to an upsurge of syphilis diagnoses among men. Between 2000 and 2001, the syphilis rate among U.S. men grew by 15%. The increases are associated with recent syphilis outbreaks among gay and bisexual men of all races in six major U.S. cities.

Put syphilis detection on your radar screen: Overall rates of primary and secondary syphilis have increased slightly for the first time in more than a decade, according to a new report from the Atlanta-based Centers for Disease Control and Prevention (CDC).[1]

Cases of primary and secondary syphilis in the United States rose from 5,979 cases in 2000 to 6,103 cases in 2001, representing an increase of 2%. The overall syphilis rate grew from 2.1 per 100,000 people to 2.2 per 100,000 people, the first such increase since 1990, according to the CDC.

In 1998, the CDC initiated efforts to eliminate syphilis from the United States, with elimination defined as the absence of sustained transmission. **(*Contraceptive Technology Update* reported on the national campaign in its September 1997 article, "Syphilis hits 40-year low; can elimination be within reach?" p. 111.)** Since those efforts began, public health officials have reported progress in combating the sexually transmitted disease (STD), states the CDC.

The increase in rates found in the new report can be attributed to an upsurge of syphilis diagnoses among men, states **Ronald Valdiserri**, MD, MPH, deputy director of CDC's HIV, sexually transmitted disease, and tuberculosis prevention programs. Between 2000 and 2001, the syphilis rate among men in the United States grew by 15%, he says. These increases are associated with recent syphilis outbreaks among gay and bisexual men of all races reported in Chicago, Los Angeles, New York City, San Francisco, Seattle, and Miami.

Any rise in syphilis can prove problematic when it comes to HIV prevention; according to the CDC, there is a two- to fivefold increased risk of acquiring HIV infection when syphilis is present.[2]

"While the goal of syphilis elimination remains unchanged, we cannot accept syphilis increases in any population as the way things are, especially since syphilis outbreaks could signal an HIV resurgence," states Valdiserri.

Some groups see drop

The new CDC reports show positive gains in the syphilis elimination campaign:

- Cases among African-Americans declined by 9.9 % (3.5% and 18.1% among African-American men and women, respectively).
- While the South continues to have the largest proportion of syphilis cases (56% of total U.S. cases), public health officials note an 8% decline in syphilis rates.
- Syphilis cases among women overall declined by 19%.

The increase in syphilis rates among gay and

bisexual men of all races pose new challenges to eliminate the disease, says the CDC. Syphilis cases among white and Latino men rose 63% and 50%, respectively, from 2000 to 2001. And while African-American males were the only men in any racial or ethnic group to experience a decline, the 3.5% decline represents a significant slowdown from the 15% drop reported from 1999 to 2000.

Heighten STD awareness

The CDC is working with local communities and health departments on new and aggressive strategies to control syphilis, states **Jo Valentine**, MSW, National Syphilis Elimination Program coordinator. In addition to rapid response teams, CDC is conducting research into possible factors underlying outbreaks and will use this data to guide intervention efforts, she says.

In focusing on outreach to the gay and bisexual male population, the CDC is developing new primary and secondary prevention approaches, including Internet-based health education and community-based syphilis screening events to alert men to the dangers of syphilis and increase early access to care, says Valentine. Expanded surveillance, including enhanced behavioral surveillance and improved health communications also is being introduced, she notes.

To better understand why gay and bisexual men may be vulnerable to syphilis, CDC has conducted studies in several cities to identify factors that may be playing a key role in syphilis transmission.[3-8]

The findings reveal a lack of knowledge about STDs among men who have sex with men, limited counseling and diagnostic screening for STDs offered by health care providers, and the need for a much more concentrated and comprehensive community response.

"We cannot and should not accept an increase in syphilis cases in any population as inevitable," says Valdiserri. "The new data do make it clear that our strategies need to evolve as patterns in disease do."

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Register now for HIV prevention conference

CDC schedules July meeting

Make plans to attend the 2003 National HIV Prevention Conference July 27-30, 2003, in Atlanta. The conference, convened by the Atlanta-based Centers for Disease Control and Prevention, is co-sponsored by more than 20 public and private organizations to share effective prevention approaches and research findings.

Conference registration information is available at the official web site, www.2003HIVPrevConf.org. Registration received before June 15 is $300; after June 15, fees will be accepted on site only at $350. Registration may be made on-line or by mailing in a downloaded registration form along with payment to Convention Information Systems, 1725 Duke St., Suite 600, Alexandria, VA 22314. Confirmation of registration will be issued by mail or e-mail.

Questions about registration may be directed to the registration coordinator at (703) 548-0569, ext. 3, or via e-mail at info@2003HIVPrevConf.org. Questions about the conference may be directed to its hotline, (866) 277-6313. ■