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IN THIS ISSUE

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Are you talking to women about HPV and cervical cancer screening?

Less than 20% of women say providers have discussed cancer/HPV link

As you review which talking points to cover with your next patient, are you planning to include dialogue on the link between human papillomavirus (HPV) and cervical cancer? Chances are you're not, according to the results from a new national survey released by the Washington, DC-based Association of Reproductive Health Professionals (ARHP).

The survey results show that while 88% of women rely on their health care providers to learn about gynecological issues, only 19% say their providers have talked to them about cervical cancer and its major cause, HPV. The survey was conducted by Greenberg, Quinlan, Rosner Research of Washington, DC.

While great strides have been made in reducing the impact of cervical cancer in America, 2005 statistics from the American Cancer Society (ACS) estimate about 10,370 cases of invasive cervical cancer will be diagnosed in the United States.[1] About 3,710 women will die from cervical cancer in the United States during 2005, according to the ACS.[1]

It is now known that some strains of HPV account for most cervical

EXECUTIVE SUMMARY

According to a new survey, while 88% of women rely on their health care providers to learn about gynecological issues, only 19% say their provider has discussed the link between cervical cancer and human papillomavirus (HPV).

- About 10,370 cases of invasive cervical cancer will be diagnosed in this year in the United States. About 3,710 women will die from the disease.
- A dual test that combines a HPV DNA test with a Pap test now is indicated as a primary screening option for women 30 years of age and older. The test is not intended to substitute for regular Pap screening, nor is it intended to screen women younger than 30 who have normal Pap tests.

cancer cases; in the United States, HPV 16 alone accounts for more than half of all cervical cancer cases, followed by HPV 18, 31, and 45.[2]

"It is really surprising to me that so many women don't know what the connection is between human papillomavirus and cervical cancer," says **Beth Jordan**, MD, ARHP medical director. "I think one of the key things for providers to do is to just ask: "Do you know why you're having Pap smears? Do you know what the connection is? If not, let's talk."

When and who to test?

In 2003, the Food and Drug Administration (FDA) approved the DNAwithPap, manufactured by Digene Corp. of Gaithersburg, MD, to help distinguish women at increased risk from those at very low risk of developing the disease. The test combines the company's Hybrid Capture 2 High-Risk HPV DNA test with a Pap test. **(*Contraceptive Technology Update* reported on the new test in its article, "Get ready to take cervical cancer screening to the next level," June 2003, p. 61.)**

The FDA approved the dual test as a primary screening option for women 30 years of age and older. The test is not intended to substitute for regular Pap screening, nor is it intended to screen women younger than 30 who have normal Pap tests, states the FDA.[3]

The ACS issued guidelines in 2002 calling for Pap tests beginning at age 21 or three years after a woman first has sexual intercourse.[4] Until age 30, screening should be done every year with the regular Pap test or every two years using the liquid-based Pap test. After age 30, women who have had three normal Pap tests in a row can wait two or three years for their next Pap.

Women with a negative HPV test and a normal Pap smear need not be screened again for three years. Women with a positive HPV test and a normal Pap test should be retested in six months to a year, according to the ACS guidelines.

According to the ARHP survey, women age 30 and younger, who are least at risk for cervical cancer, are most knowledgeable about its cause and more likely to discuss HPV openly with their health care professionals. However, women age 30 and older are less knowledgeable about the virus, the survey results indicate. They are more likely to have persistent, high-risk forms of HPV that can lead to cervical cancer and therefore may benefit from HPV testing along with their Pap test.[5]

HPV testing also is appropriate for the following situations:

- triage after a test result of atypical squamous cells of unknown origin (ASC-US);
- triage after colposcopy does not detect precancer in women with low-grade squamous

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Editorial Questions

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

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RESOURCE

The Association of Reproductive Health Professionals has devoted an entire issue of *Health & Sexuality* to the topic of cervical cancer prevention and HPV DNA testing. To download the publication, go to the ARHP web site, www.arhp.org. Click on "Healthcare Providers," "Online Publications," "Health & Sexuality Magazine," and "Cervical Cancer Prevention and HPV DNA Testing." Answers to frequently asked questions about HPV are on pp. 11-12.

intraepithelial lesion (LSIL);

• testing one year after known cervical intraepithelial neoplasia (CIN-1) biopsy;

• testing the cervix after cryosurgery or a loop electrosurgical excision procedure (LEEP) to treat precancerous dysplasia;

• HPV testing for anal lesions.[6]

"In our study of 338 women undergoing screening for cervical cancer, only 34% of women were aware that HPV testing was a part of the follow-up for an abnormal Pap test," says **Carmen Radecki Breitkopf**, PhD, assistant professor in the department of obstetrics and gynecology at the University of Texas Medical Branch in Galveston.

Check Pap knowledge

Breitkopf and her fellow researchers questioned women undergoing cervical screening at two Texas clinics to evaluate their knowledge and informational needs about Pap testing.[6]

Results of their study indicate that minority women and those of low socioeconomic status had poor understanding of Pap testing.[7] Identifying misunderstandings and improving patient education on the most basic aspects of Pap testing may increase adherence to follow-up when abnormalities are detected, researchers conclude.[7]

Despite the benefits of Pap test screening, not all American women take advantage of it, according to the ACS. Between 60% and 80% of American women with newly diagnosed invasive cervical cancer have not had a Pap test in the past five years, and many of these women have never had a Pap test.[8] In particular, elderly, African-American, and low-income women are less likely to have regular Pap tests, says the ACS.[8]

Why aren't clinicians talking to women about cervical cancer and HPV?

"The communications gap between providers and patients related to cervical cancer and HPV is an issue that is largely due to time constraints and a reluctance to discuss a sexually transmitted infection with women," says Jordan. "But because new techniques, including improved types of diagnostic testing, now make cervical cancer a disease that can be better prevented, we're encouraging women to discuss with their health care provider their HPV risk, get regular screenings with the Pap test and, if they are age 30 or older, ask about HPV testing as well." **(ARHP has prepared answers to frequently asked patient questions on HPV. Check the resource box, left, for directions on how to access them.)**

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NuvaRing not affected by heavier body weight

The next patient in your exam room is in her mid-20s. While she is in generally good health, you note she weighs in at 210 pounds. What contraceptive methods do you offer her?

The contraceptive vaginal ring (NuvaRing, Organon, West Orange, NJ) may be an acceptable

EXECUTIVE SUMMARY

New research indicates that the efficacy of the NuvaRing contraceptive vaginal is not affected by heavier body weight, and it protects all women against pregnancy for an entire month.

- Study results suggest that NuvaRing provides similar contraceptive efficacy for all women, including heavier women weighing 189 to 272 pounds.
- Help heavy women to choose contraception by weighing the risks of contraception vs. the risks of pregnancy in the absence of contraception. The best contraceptive method is the one that is medically appropriate and is used every time by someone happy with the method.

option. New research presented at the annual clinical meeting of the American College of Obstetricians and Gynecologists (ACOG) indicates that the ring's effectiveness is not affected by heavier body weight.[1] Results from the body weight analysis indicate that contraceptive efficacy was similar in all women, including heavier women weighing 189 to 272 pounds.[1]

"Based on the data we have thus far, NuvaRing seems a reasonable choice for women of any weight," says the paper's presenter, **Carolyn Westhoff**, MD, MSc, professor of obstetrics and gynecology and public health at Columbia University in New York City.

Can weight be a factor?

Research has looked at the impact of weight on efficacy in other forms of contraception. In the case of the transdermal contraceptive (Evra, Ortho McNeil Pharmaceutical, Raritan, NJ), its labeling states that the method may be less effective in women at or above 198 pounds than in women with lower body weights. This precaution stems from an analysis of pooled data from three pivotal studies that indicates while contraceptive failure was low and uniformly distributed across the range of body weights in women below 198 pounds, in women at or above that weight, contraceptive failures may be increased.[2]

Two recent epidemiologic studies have found that being overweight may increase a woman's risk of becoming pregnant while using oral contraceptives (OCs).[3,4] Given the progressively higher prevalence of overweight and obesity in the United States in recent years, these results suggest that elevated body mass index (BMI) may be an increasingly important cause of unintended pregnancy among OC users, says **Victoria Holt**, PhD, MPH, a professor in the department of epidemiology at the University of Washington in Seattle who served as lead author for both studies. **(More research is needed on the subject before clinicians change their prescribing habits, according to the *Contraceptive Technology Update* article, "Does increased weight impact OC efficacy," April 2005, p. 45. Also review the *CTU* article, "Does weight play a role in effectiveness?" July 2002, p. 81.)**

The body weight data presented at the ACOG meeting came from a secondary analysis of the efficacy findings from the NuvaRing Phase III clinical database.

The distribution of pregnancies by subjects' baseline body weight was analyzed by deciles for the intent-to-treat (ITT) and per-protocol (PP) populations. In total, 27 pregnancies occurred among 3,259 women in the ITT group (0.83%) and 12 pregnancies occurred in the 2,788 women in the PP group (0.43%). Pregnancies were evenly distributed over the baseline body weight deciles, demonstrating that NuvaRing was not associated with an increased risk of pregnancies in heavier women.[1]

Help women choose

As the authors of *Contraceptive Technology* advise, the best contraceptive method is the one that is medically appropriate and is used every time by someone happy with the method.[5] As pointed out in a recent editorial, for women with medical problems, a useful formula for contraceptive choices weighs the risks of contraception vs. the risks of pregnancy in the absence of contraception.[6] Using this approach, highly effective contraception often emerges as a priority for very heavy women.[6]

Effects of a birth control method on menses may be very important to a woman.[5] Results from a controlled trial of women randomized to using an oral contraceptive or NuvaRing compared bleeding patterns for an 84-day period following immediate initiation of either method.[7] Investigators found that the ring users experienced fewer days or episodes of bleeding-spotting and shorter intervals.[7]

"The women on NuvaRing had better bleeding patterns than those on the Pill; at the end of the study, the women on NuvaRing were much more likely to continue than women on the Pill," says Westhoff, who served as the paper's lead author.

Westhoff uses what has been termed the "Quick Start" approach to initiating contraception, whereby

women initiate their chosen birth control method at the provider's office, regardless of where they are in their monthly cycle.[8,9] Women had no trouble in beginning use of the vaginal ring in the office, Westhoff states.

"I think a lot of doctors worry that women are nervous about using NuvaRing," she observes. "We did not see that."

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New IUDs may expand contraceptive choices

Where does intrauterine contraception fit in the array of family planning choices you offer your patients? If you never or rarely perform intrauterine device (IUD) insertions, new devices now under development may lead you to give the method a second look.

The Belgian research organization Contrel is testing a T-shaped levonorgestrel-releasing intrauterine system (IUS), which it has trademarked as Femilis, with a smaller version for nulliparous women trademarked as Femilis Slim. Both devices release a daily dose of 20 mcg levonorgestrel, similar to the currently available Mirena IUS (Berlex, Montville, NJ.) Femilis is in clinical development for the treatment of menorrhagia, for endometrial suppression during estrogen replacement therapy, and for contraception, states **Dirk Wildemeersch**, MD, founder of Contrel.

EXECUTIVE SUMMARY

The Belgian research organization Contrel is now testing Femilis, a T-shaped levonorgestrel-releasing intrauterine system (IUS), with a smaller version for nulliparous women trademarked as Femilis Slim. Both devices release a daily dose of 20 mcg levonorgestrel, similar to the currently available Mirena IUS.

- Two other intrauterine devices from Contrel include the GyneFix, a frameless IUD, which is available in Europe and China, and the FibroPlant-LNG, a levonorgestrel-releasing IUS, which is in development.
- Based on the same design as the GyneFix IUD, the FibroPlant-LNG delivers a daily dose of 14 mcg levonorgestrel.

T-shaped IUDs have been used for several decades. Health care providers are familiar with their insertion, and fitting requires minimal training, he reports. The combination of drug delivery technology with a conventional IUD frame is therefore attractive for use by such nonspecialist providers as nurses, midwives, and general practitioners, as well as those who are not inserting IUDs on a regular basis, he states. Femilis is especially designed for this target group of health care provider, says Wildemeersch. While Femilis utilizes a push-in technique, Mirena is released into the uterus by pulling back a "slider" mechanism.

"To minimize problems at insertion, an easy and safe push-in technique has been developed," he states. "The simplicity of this technique may make the method more accessible to women in remote places."

Review the research

Research has just been published on the ease of insertion, contraceptive efficacy, and safety of the two Femilis designs, as well as an analysis of the impact of the Femilis IUS on menstrual blood loss in women with and without menorrhagia.[1,2]

In the first study, 142 parous women were fitted

with the Femilis device, with 92 women receiving the Femilis Slim device. The devices were inserted using the simplified push-in technique. Insertion was reported as "easy" in 97.9% of all women; pain at insertion was absent in 24.7% of study participants and described as "mild" in 67.7% of women.[1]

At the time of study analysis, 76 women had the Femilis IUS in place for periods in excess of one year. No pregnancies had been observed, investigators report. There was one expulsion in the nulliparous group and one in the parous group. Ten removals, mainly for bleeding and pain, were performed for medical reasons. One pelvic infection, caused by *Chlamydia trachomatis*, occurred in a nulliparous woman. The infection was resolved without removing the IUS. No other serious adverse events were reported.[1]

In the second published study, 60 women used the Femilis IUS for four to more than 30 months, with investigators analyzing menstrual blood use using the visual assessment technique. Twenty-eight women had normal menstrual periods at baseline, and 32 women had idiopathic menorrhagia.

Study findings indicate that menstrual blood loss scores dropped significantly during the observation period in almost all the study participants. The median menstrual score at baseline in women with normal menstrual bleeding was 140 (range 80-160) and dropped to a median score of 5 (range 0-150) at follow-up, resulting in a decrease of 96%.

In the 32 women with menorrhagic bleeding at baseline, menstrual flow dropped from a median score of 232 (range 185-450) at baseline to a median score of 3 (range 0-50) at follow-up, which is a decrease of 99%. Twenty women developed amenorrhea (33%), which was distributed equally among the normal/menorrhagic groups.[2]

The impact on menstrual blood loss of the Femilis system confirms other studies with devices releasing the same or lower amounts of levonorgestrel.[3] The device's impact in suppressing the endometrium could offer a health benefit and improvement in quality of life, particularly in women with heavy bleeding and anemia, the researchers conclude.[2]

Contrel also has developed the GyneFix, a frameless IUD, which is available in Europe and China. The device's design consists of several copper cylinders tied together on a string and is anchored 1 cm deep into the top of the uterus.[4] Its design is intended to cause less pain and bleeding than framed devices.[5] **(*Contraceptive Technology Update* reported on the IUD in its article, "FDA approval sought for frameless, flexible IUD," April 1999, p. 41.)** It is not yet available in the United States. It could be marketed in the U.S. in cooperation with a suitable partner, says Wildemeersch.

The company also is developing FibroPlant-LNG, a levonorgestrel-releasing IUS. Based on the same design as the GyneFix IUD, it delivers a daily dose of 14 mcg levonorgestrel. Initial studies indicate that the device may be highly acceptable and be effective in reducing bleeding.[6,7]

"A greater variety of intrauterine systems will encourage use by women who have been denied this safe and effective method: younger women and those who have not had children," says **Philip Darney**, MD, MSc, professor of obstetrics and gynecology at University of California, San Francisco, and chief of obstetrics, gynecology, and reproductive sciences at San Francisco General Hospital. "These new systems will also treat conditions like abnormal uterine bleeding, uterine myomata, and endometriosis, making risky surgery less common just as current intrauterine contraceptives have made sterilization operations less frequent." **(Review IUD options in the United States; see the *CTU* article, "Are you offering enough information on IUD use," June 2005, p. 69.)**

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Research eyes new sterilization option

Investigators now are looking at a transcervical sterilization option that, if proven safe and effective, will give women another alternative for permanent contraception.

The treatment phase for the Adiana system, now under development by the Redwood City, CA-based Adiana, recently has been completed at 14 centers in the United States and two international centers. All treated patients are being monitored, and the trial's primary clinical endpoint — pregnancy prevention at one year — will be established at the appropriate statistical confidence interval, reports **Paul Goeld**, Adiana's president and chief executive officer. The company expects to file a pre-market approval application with the Food and Drug Administration (FDA) in mid-2006, he reports.

Tubal sterilization is one of the leading contraceptive options for American women. In 2002, 27% of all contracepting U.S. women relied on the method.[1] Of the 700,000 annual bilateral procedures, about half are performed postpartum and half as ambulatory interval procedures.[2]

Until November, 2002, no hysteroscopic method of tubal interruption had ever been approved by the FDA. With the advent of the Essure transcervical sterilization method, expect to see advances in these types of procedures, says **Amy Pollack**, MD, MPH, senior lecturer in the Mailman School of Public Health at the New York City-based Columbia University. **(Review information on the Essure procedure; see the *Contraceptive Technology Update* articles, "Changes in store for sterilization method," August 2005, p. 91, "Women who want permanent birth control now have second option," January 2003, p. 1, and the *Contraceptive Technology Reports* supplement, "Sterilization in the office: The concept is now a reality," inserted in the February 2003 issue.)**

EXECUTIVE SUMMARY

Scientists are examining the Adiana procedure for female sterilization. According to its developers, the procedure requires no incisions and can be performed under local anesthesia in a physician's office.

- The Adiana procedure uses a catheter-based system to deliver a short burst of temperature-controlled radiofrequency energy to each fallopian tube followed by placement of a soft, porous biomaterial. The catheter is delivered through a thin hysteroscope that is placed through the vaginal canal and into the uterine cavity.
- The biomaterial remains implanted within the fallopian tube, where surrounding tissue grows into it over a few weeks. This growth results in permanent and total occlusion of the tube.

Review the procedure

Adiana was founded in 1997. It took approximately two years to develop Adiana's technology, followed by three years of pilot clinical studies to refine its product design, says Goeld. An application for a formal clinical trial was filed with the FDA in late 2002. That trial still is ongoing, he adds.

The Adiana procedure is performed in two steps; first, a catheter is delivered through a hysteroscope into the intramural portion of the fallopian tube. Using low-level bipolar radiofrequency energy, a superficial lesion is created to remove surface epithelium. The second step calls for placing a matrix (a porous, nonbiodegradable implant material) into the lesion. The matrix remains implanted within the fallopian tube, where surrounding tissue grows into it over a few weeks. The ingrowth results in permanent and total occlusion of the fallopian tube.[3] Alternative contraception is used for three months followed by determination of tubal occlusion by hysterosalpingography.

In a poster presentation at the recent annual clinical meeting of the Washington, DC-based American College of Obstetricians and Gynecologists, investigators reported no serious adverse events within the first 500 women treated in the device's multicenter trial.[4] Mean procedure time ("scope in to scope out") was fewer than 15 minutes, investigators noted. Local anesthesia without sedation was used in most patients. Women were "highly satisfied" with the procedure and many returned to their usual activities the same day. Preliminary results indicate the procedure is safe and effective, but more follow-up is required.

More research needed

The compact size of Adiana's implant material, described as "smaller than a grain of rice," results in its ability to reside entirely within the patient's fallopian tube. Since the implant material does not protrude into the uterine cavity, it may be advantageous for those women who would seek

to reverse their permanent birth control through in vitro fertilization, observes Pollack. More research will need to be conducted in the matter to see if that claim is valid, she says.

Transcervical sterilization is particularly of interest because it allows the user to avoid a transabdominal surgical procedure, notes Pollack.

However, the need for use of special equipment in the form of a hysteroscope presents a challenge in implementing transcervical sterilization into current practice, she states. More focus will need to be given in training medical residents and providing continuing education for practicing physicians in use of outpatient hysteroscopy, says Pollack.

"In the past, there just hasn't been that much use of it," she notes. "It's been used as a diagnostic procedure; much of the demand for it has been in the private sector, where residents don't get as much experience."

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Teens & dysmenorrhea: Look to low-dose OCs

The 15-year-old young woman in your exam room tells you that she has crampy pelvic pain that begins shortly before or at the onset of her menstrual period that lasts one to three days. She says she usually misses a day of school each month due to the pain. What is your next move?

Primary dysmenorrhea, or painful menses in women with normal pelvic anatomy, usually begins during adolescence.[1] Some 20% to 90% of all female adolescents experience dysmenorrhea,[2-4] and it is the leading cause of recurrent short-term school absenteeism in U.S. adolescent girls.[3,5]

New research indicates that today's low-dose (20 mcg) oral contraceptives (OCs) are an effective treatment choice for moderate to severe dysmenorrhea in adolescents.[6] The research offers one of the first looks at use of current pills; earlier studies focused on use of higher-dose pills.[7]

EXECUTIVE SUMMARY

New research indicates that today's low-dose (20 mcg) oral contraceptives (OCs) are an effective treatment choice for moderate to severe dysmenorrhea in adolescents.

- Some 20% to 90% of all female adolescents experience dysmenorrhea; it is the leading cause of recurrent short-term school absenteeism in U.S. adolescent girls.
- Combination OCs can have a beneficial effect on conditions that can affect teens' quality of life, including benign breast disease, functional ovarian cysts, iron deficiency anemia, acne, and menstrual irregularity.
- Nonsteroidal anti-inflammatory drugs are effective in inhibiting prostaglandin synthesis and decrease the volume of menstrual flow.

While nonsteroidal anti-inflammatory medications represent an effective course of treatment for painful menstrual cramps in teens, birth control pills have the added benefits of treating or preventing three common conditions in female adolescents: irregular bleeding, acne, and unintended pregnancies, reports **Andrew Kaunitz**, MD, professor and assistant chair in the Department of Obstetrics and Gynecology at the University of Florida Health Science Center/Jacksonville.

Teenagers may especially benefit from using the Pill for treatment of dysmenorrhea, since they seem to have more burden of pain and disability from dysmenorrhea than older women, observes **Anne Davis**, MD, assistant professor of obstetrics and gynecology at Columbia Presbyterian Medical Center in New York City and lead author of the current research.

Review the research

The new study reports the results of a randomized, double-blind, placebo-controlled clinical trial of 76 healthy adolescents age 19 or younger with moderate or severe dysmenorrhea. The teens were randomly allocated to receive a 20 mcg ethinyl estradiol OC or a matching placebo for three months, and they were allowed to use their usual pain medications as needed during the trial.

By cycle three, OC users reported fewer days of

any pain, fewer days of severe pain, and fewer hours of pain on the worst pain day than placebo users; however, these differences did not reach statistical significance, state the researchers.[6] No serious adverse events related to Pill use were noted. Two teens in the pill group discontinued use due to such side effects as nausea and acne. One teen using the placebo stopped treatment due to moodiness.

Pills are effective in relieving primary dysmenorrheal. Most women have moderate to complete relief within a few months after starting OC use.[8] Teens who experience relief from menstrual cramping are more likely to use the Pill consistently and correctly.[9]

But do teens know of the Pill's noncontraceptive benefits? According to a 1998 survey, half of the respondents were not aware of any OC benefits beyond preventing pregnancy.[10]

Remind teens that combination OCs can have a beneficial effect on a number of conditions that can affect their quality of life, including benign breast disease, functional ovarian cysts, iron deficiency anemia, acne, and menstrual irregularity.[11] Also, tell teens that pills are just as safe in adolescents as they are in older women, says Davis.

How about new methods?

How do new methods such as the transdermal contraceptive (Evra, Ortho-McNeil Pharmaceutical, Raritan, NJ) impact primary dysmenorrhea in teens? Results from a small study of adolescent girls using the contraceptive patch indicate that about 40% reported a decrease in dysmenorrhea symptoms.[12]

More research needs to be conducted to determine if the contraceptive patch and ring provide similar efficacy in relieving the condition, says Kaunitz.

Teens who are not good candidates for hormonal contraception may look to nonsteroidal anti-inflammatory drugs for relief of dysmenorrhea.[13] These drugs are effective in inhibiting prostaglandin synthesis and decrease the volume of menstrual flow.[1]

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New compounds eyed for male contraception

The push is on to develop an effective male contraceptive, with almost $8 million from the National Institutes of Health (NIH) going to researchers at the University of Kansas in Lawrence and the University of Kansas Medical Center in

EXECUTIVE SUMMARY

Scientists are moving forward with research to develop new compounds that may be effective in male contraception.

- Researchers are looking at several compounds and targeting those which temporarily deactivate key enzymes to inhibit sperm development or motility. Gamendazole has been shown to cause temporary infertility in male rats.
- Adjudin (AF-2364) is a promising candidate for male contraception. Early research in male rats indicates that it does not affect the hypothalamic-pituitary-testicular axis.

Kansas City toward identifying potential chemical compounds for such use.

Several compounds to be studied

The five-year contract, issued through the Contraceptive and Reproductive Health Branch of the NIH's National Institutes of Child Health and Human Development, will allow the Kansas scientists to pursue research and testing started in partnership with the NIH four years ago. The research team headed by Gunda Georg, PhD, distinguished professor of medicinal chemistry at University of Kansas, includes Ernst Schonbrunn, PhD, assistant professor and X-ray crystallographer, and Qizhuang Ye, PhD, director of the High Throughput Screening facility, both at the University of Kansas, and **Joseph Tash**, PhD, associate professor and a reproductive biologist at the University of Kansas Medical Center. The team will be look at several compounds and targeting those that temporarily deactivate key enzymes to inhibit sperm development or motility.

During their previous work with the NIH, the Kansas researchers identified a chemical compound, now known as Gamendazole, which caused temporary infertility in male rats by affecting sperm production. Designed through structure activity studies based on the lead compound, lonidamine, Gamendazole was the most promising analog in terms of potency and lack of side effects, says Tash, the lead reproductive biologist on the contract effort for the contraceptive work. Investigators are planning to publish research on the compound soon, he states.

The Kansas researchers hope to conduct detailed preclinical studies of Gamendazole's toxicology, dosing, and stability, reports Tash. Upon completion of such studies, clinical trials of the compound could begin in three to five years, he notes.

Other research in works

Research stemming from lonidamine is offering potential results in the male contraceptive field for scientists at the Population Council, a New York City-based research organization. **C. Yan Cheng**, PhD, a biochemist and molecular biologist, and other council investigators began looking at candidate compounds from lonidamine, an anticancer drug, when research indicated that one side effect of the drug was a temporary disruption of spermatogenesis. While lonidamine itself could not be used as a contraceptive due to its toxic side effects, Cheng's team began looking at nontoxic analogues of lonidamine with an eye toward their use in male contraception.[1-6]

With funding from the NIH, the Population Council scientists have identified one compound, AF-2364 or Adjudin, as a promising candidate for male contraception. Early research in male rats indicates that it does not affect the hypothalamic-pituitary-testicular axis.[7,8] Researchers are developing a testis-specific delivery system to target Adjudin to the testis so that the action of Adjudin can be limited to the cells behind the blood-testis barrier in the seminiferous epithelium. Why?

"First, a very low dose of Adjudin will be needed for its administration since it is being targeted to cells in the seminiferous epithelium to perturb cell adhesion function there; as such, the mild toxicity issue associated with this compound can be overcome," observes Cheng. "Second, this delivery system can be developed into a therapeutic approach to treat disease behind the blood-testis barrier, such as testicular cancer."

Will it work in a pill?

Will Adjudin be effective in oral administration when it comes to male contraception? Cheng says so; he notes that it does not interfere with the hypothalamic-pituitary-testicular axis, so the physiological events that are dependent on androgens are not affected. Furthermore, it does not interfere with the serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels in addition to testosterone.

This finding is significant because it illustrates

COMING IN FUTURE MONTHS

- DMPA-SC self-administration: Would women give it a shot?
- Abortion: Numbers continue to decline
- New recommendation: Voluntary HIV testing for all pregnant women
- Short-term Pill use can cut ovarian cancer risk
- Male circumcision may lessen HIV risk

this compound does not interfere with the male hormones, Cheng points out.

Adjudin apparently exerts its effects largely on the Sertoli-germ cell adhesion function, thereby inducing premature loss of germ cells from the seminiferous epithelium, he observes. Since this effect occurs locally in the testis, general toxicity, if any, is minimal, Cheng notes. This lack of toxicity is crucial for a successful male pill, since men likely will take such a pill over a long period of time for contraceptive benefits, states Cheng.

If a potent agent such as Adjudin can be targeted specifically to the site of action, this will likely reduce its toxicity to a minimum, he says. "At present, we're using Adjudin to develop an *in vivo* model to study cell adhesion function in the testis," Cheng explains. "We have identified several signaling pathways that are being activated to regulate junction restructuring, and recently published findings from our laboratory have shown that their inactivation can indeed affect cell adhesion function in the testis."[9]

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CTUPDATES
News ■ Resources ■ Events

Make plans now to attend fall conference

Register now for the annual *Contraceptive Technology*: Quest for Excellence conference, scheduled for Oct. 27-29, 2005, in Atlanta.

The conference will cover such topics as new modes of delivering hormonal contraceptives, improved versions of intrauterine contraceptives, and upcoming contraceptives. Preconferences on Oct. 27 will cover health care for women older than 40 (Preconference A), intrauterine device insertion training (Preconference B), and endometrial biopsy skill-building for clinicians (Preconference C). Continuing education credits are available.

Early fee deadline is Sept. 15. Early preconference fees for all attendees are $195 for Preconference A, $105 for Preconference B, and $95 for Preconference C; regular Preconference fees are $235, $135, and $125, respectively. Early fees for the main conference are $475 for physicians and $375 for nurse practitioners, physician assistants, and others; regular fees are $515 and $415, respectively.

To register on-line, go to Contemporary

CE/CME Instructions

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

Forums at www.cforums.com. Click on "Conferences," then "*Contraceptive Technology*: Quest for Excellence." Registration also may be made by calling (800) 377-7707, ext. 3, Monday-Friday, 8 a.m.-5 p.m. Pacific Time, or by faxing a completed registration form to (800) 329-9923. ■

CE/CME Questions

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

- **Identify** clinical, legal, or scientific issues related to development and provisions of contraceptive technology or other reproductive services. (See "**New IUDs may expand contraceptive choices,"** "**Research eyes new sterilization option,"** and **"New compounds eyed for male contraception.")**
- **Describe** how those issues affect service delivery and note the benefits or problems created in patient care in the participant's practice area.
- **Cite** practical solutions to problems and integrate information into daily practices, according to advice from nationally recognized family planning experts. (See **"Are you talking to women about HPV and cervical cancer screening?")**

9. What type of human papillomavirus accounts for more than half of all cases of cervical cancer in the United States?

A. Type 16
B. Type 18
C. Type 31
D. Type 45

10. The Femilis levonorgestrel-releasing intrauterine system now under development by Contrel releases what daily dose of levonorgestrel?

A. 15 mcg
B. 20 mcg
C. 25 mcg
D. 30 mcg

11. The Adiana sterilization procedure relies on use of which of the following medical equipment?

A. Laparoscope
B. Hysteroscope
C. Microscope
D. Colposcope

12. What anticancer drug has yielded analogs that may be used in male contraception?

A. Diazepam
B. Doxorubicin
C. Lonidamine
D. Epirubicin

Answers: 9. A; 10. B; 11. B; 12. C.

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