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Vaginal microbicides needed for female-controlled prevention

Products to help women protect against HIV/AIDS

By the end of the century, women will outdistance men in the numbers of those living with HIV infection.[1] To combat the increasing risk, women need more options for prevention. While the search continues, no "magic bullet" has emerged, notes **Michael Rosenberg**, MD, MPH, clinical professor of OB/GYN and epidemiology at the University of North Carolina and president of Health Decisions, a private medical research firm, both in Chapel Hill.

"Why has the search been going on now for more than 10 years, and we're no closer to this than we were at that time?" he asks. "How well will this magic bullet will perform in relation to what we now have, nonoxynol-9 [N-9], plus some others?"

Male condoms greatly reduce disease transmission, but they must be used correctly and consistently to offer protection, and their use is ultimately outside the control of women. Female condoms represent a barrier method that women can choose to use, but because the condoms' outer rings are visible, they may cause problems for women whose partners object to condom use.

New supplement for NPs enclosed

As a bonus for our *Contraceptive Technology Update* readers, this month's issue includes a free quarterly supplement, *NP Clinical Update*. *NP Clinical Update* will cover clinical issues of interest to nurse practitioners, including reports on the latest credible scientific research regarding treatment of medical problems, health risks, medications, prescription practices, and infectious diseases, including sexually transmitted diseases. We'll also cover new clinical guidelines, history taking, health screenings, and midlife issues such as post-menopausal hormones. Patient education handouts will be a regular feature. Don't miss the handout, "Human Papillomavirus and Genital Warts," enclosed in this issue.

We hope you enjoy this new addition to *CTU.*

EXECUTIVE SUMMARY

Women across the globe face a growing risk of HIV infection. To combat this risk, research is focusing on vaginal microbicides to give women another female-controlled method of protection against HIV and other sexually transmitted diseases (STDs).

- In lab tests, spermicides containing nonoxynol-9 (N-9) have proven lethal to organisms that cause gonorrhea, genital herpes, trichomoniasis, syphilis, and HIV. But their disruptive effect on the vaginal epithelium clouds the issue of their use.
- The ideal microbicide should be effective against HIV/STDs, non-irritating, long-acting, inexpensive, easily available, and easy to use. It should be available in spermicidal and non-spermicidal formulations.

Vaginal microbicides represent a preventive option that women can control easily. They do not require negotiation or consent from a partner. With such a "stealth" method, women gain another method to fight the war against AIDS.

Several products are in the research pipeline, and some use the spermicide nonoxynol-9 or other surfactants. Others include acid buffering gels; natural products such as *lactobacillus crispatus*, antimicrobial peptides, magainins, or plant extracts; inhibitors of viral entry; post-binding fusion inhibitors; and reverse transcriptase inhibitors.

N-9 and its role

Most American women are familiar with products containing the N-9 spermicide. It is available in several over-the-counter formulations, including foam, jelly, cream, film, and gel. Some believe the shortest path to introduction of a microbicide is to prove in clinical trials that N-9 spermicides are effective against HIV and sexually transmitted disease (STD) transmission.

"I think it's felt that we could get a spermicide on the market faster than we could get a product that has an HIV or STD indication because you could do the spermicidal studies more quickly," observes **Zeda Rosenberg**, ScD, senior scientist for prevention research with the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, MD. "It is true you could get a spermicide on the market; however, you couldn't suggest that anyone use that for STD or HIV prevention until you did the efficacy studies." (Spermicides with N-9 are now under clinical review for contraceptive effectiveness, which will end reliance on decades-old data. **See *Contraceptive Technology Update,* January 1999, p. 5.**)

What about vaginal irritation?

Concerns about N-9's potential for vaginal irritation cloud the issue of its use in HIV/STD prevention. While N-9 is a surfactant that destroys the sperm cell membrane, frequent use has been associated with vaginal epithelial disruption.[2]

In the lab, N-9 is lethal to organisms that cause gonorrhea, genital herpes, trichomoniasis, syphilis, and HIV.[3] However, a study published last year showed the use of a N-9 vaginal film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection in a group of sex workers who used condoms and received STD treatment.[4]

"I don't think we have answered the question whether N-9, in a higher dose, in a better formulation, works," remarks Zeda Rosenberg. "I think that keeping an open mind on this, the study needs to be done. Given that there are varying spermicidal capabilities of different N-9 formulations, it could very well be that the formulation is the crucial component here."

A Phase III trial sponsored by The Joint United Nations Programme on HIV/AIDS (UNAIDS) of Geneva, Switzerland, is examining the efficacy of a N-9 gel in HIV/STD transmission. Scientists with the Population Council in New York City are looking at use of N-9 in conjunction with carrageenan, a compound derived from red seaweed, in prevention of HIV and other STDs. Researchers are testing carrageenan alone and in tandem with N-9 in developing a spermicide that will protect against HIV while maintaining the same protection against pregnancy.[5]

COMING IN FUTURE MONTHS

- OCs risks cancel out after 10 years
- Vaccine under research for human papillomavirus
- Two-rod Norplant implant system: Will U.S. see it?
- Mifepristone before the millennium
- Products for management of menopausal symptoms

What are the ideal characteristics for a new microbicide? According to Zeda Rosenberg, they include the following:

- active against a range of STD-causing pathogens;
- not irritating to mucosal surfaces;
- available in both spermicidal and non-spermicidal formulations;
- acceptable (color, taste, lubricity, portability, and "stealth factor");
- biodiffusible;
- bioadhesive;
- absence of systemic absorption;
- long-acting;
- stable at high temperatures;
- able to maintain or enhance normal vaginal ecology.

Add "inexpensive" and "available without a prescription" to the wish list as well, suggests a similar UNAIDS listing.[6]

Study: Odorless cream preferred

A study involving more than 600 Brazilian women examined their preferences regarding a vaginal antimicrobial contraceptive.[7] Most women indicated they would prefer a cream rather than a suppository, with no taste, odor, or color, or at least a light color. Its application should precede intercourse, be done with an applicator, and last for more than eight hours. Such a method would offer protection against pregnancy, as well as against HIV and STDs.

Several challenges face researchers as they test new topical microbicides. There is insufficient knowledge on vaginal transmission of HIV and other STD pathogens, as well as limited understanding of cervico-vaginal and intercourse physiology, human sperm biology, and fertilization. There also is no well-established correlation between in vitro, animal models, and clinical testing. A lack of optimal formulations and technical issues such as amount, purity, and solubility add to the challenge.

It also is difficult to independently assess the efficacy of the microbicide in the trial without compromising current recommendations to include condoms with every act of intercourse. In the study on N-9 film, a majority of sex workers who were counseled to use condoms were able to do so with their paying clients.[4] There is a move to test more populations of women in primary partnerships, rather than commercial sex workers, Zeda Rosenberg says. These women would receive intensive education on condom use in a run-in phase prior to the microbicide trial. Those who continue failing to use condoms at least half the time would be trial candidates.

Microbicides should be available in spermicidal and non-spermicidal forms so women who desire to become pregnant can safely do so without risk of HIV / STD infection. Researchers also are looking at rectal use of microbicides for use in heterosexual couples who engage in anal intercourse, as well as in men who have sex with men.

"It's a great idea to do combination microbicides," notes Zeda Rosenberg. "We are working with forging liaisons between companies, because some companies have great formulations, and some companies have good-looking active ingredients."

Whether products protect against pregnancy and HIV, HIV alone, or against specific STDs, the time is now for their emergence, says **Daniel Malamud**, PhD, professor of biochemistry at the University of Pennsylvania and vice president of research and development at Biosyn, both in Philadelphia. Biosyn is working with C31G, a family of molecules with broad-spectrum capabilities.

"I think you want a broad spectrum, but if it is easier to get one that is HIV-specific, which is the real crisis now, I would certainly support that," he notes. **(*CTU* will offer an overview of microbicide products in the research pipeline in the April issue.)**

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Progestin-only ECPs on the way to the U.S.

With the first dedicated emergency contraceptive pills (ECPs) now on American market shelves, two companies are pursuing introduction of progestin-only pills for the same application.

Gynétics of Somerville, NJ, manufacturer of the Preven Emergency Contraceptive Kit, has begun multinational Phase III clinical trials on a levonorgestrel product, according to **Ellyn Caravetta**, a spokeswoman for the company. Prevent was the first dedicated combined hormonal EC product approved by the U.S. Food and Drug Administration (FDA). Approval of the levonorgestrel product in the United States and Canada is expected later this year or in early 2000.

Women's Capital Corp., based in Seattle and Washington, DC, completed its New Drug Application in January for submission to the FDA, reports **Sharon Camp**, PhD, company president. "We hope to receive priority review status of six months or less, which would allow us to launch the product sometime this year," she says. "We expect to submit an application in Canada in the first part of this year."

The FDA has affirmed the safety and efficacy of the Yuzpe regimen for emergency contraception. The Preven kit follows the Yuzpe regimen, using four pills, each containing 0.05 mg ethinyl estradiol and 0.25 mg levonorgestrel. **(Read more about the Preven kit and about progestin-only ECPs *in Contraceptive Technology Update,* November 1998, p. 141.)**

Officials at Gynétics and Women's Health Corp. are interested in pursuing dedicated progestin-only products after an international study last year demonstrated the advantages of a levonorgestrel-only emergency contraceptive over the Yuzpe regimen.

The study found that the levonorgestrel-only method was more effective and resulted in less nausea and vomiting than the combination regimen.[1] The overall method failure rate (the percentage of women who became pregnant in spite of taking the treatment) was higher in the group using the Yuzpe regimen (3.2%) than in the progestin-only group (1.1%)

85% of pregnancies prevented

Calculations of the number of pregnancies that could have occurred if no treatment had been given showed the levonorgestrel method prevented 85% of unintended pregnancies, compared with 57% for the Yuzpe regimen. The trial was coordinated by the Special Programme of Research, Development, and Research Training in Human Reproduction, a division of the World Health Organization in Geneva, Switzerland.

"There are data on nearly 2,000 women in 21 study centers in 14 countries, including the U.S. and Canada, where we will market the product," Camp says about the study. "We are also providing supporting data from an earlier Hong Kong comparative study of over 840 women[2] and 35 smaller clinical studies of levonorgestrel from postcoital contraception."

According to company officials, Gynétics plans to market the levonorgestrel pills with a step-by-step patient information book and a home pregnancy test. Women's Health Corp. plans to market its product without a pregnancy test, says Camp.

The Preven kit is now available by prescription in more than 25,000 leading drug stores. The company anticipates Medical approval this month, with all states offering Medicaid reimbursement, except for Idaho and North Dakota.

Nearly 6,000 calls have been placed to the company's toll-free number, 888-PREVEN2, and more than 500,000 "hits" have been recorded on the product's Web site, www.PREVEN.com. The most frequented areas are pages reviewing the

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The first dedicated emergency contraceptive pill (ECP) product in the United States may be joined soon by two more progestin-only entities. Gynétics of Somerville, NJ, and Women's Capital Corp. of Seattle and Washington, DC, are seeking approval of levonorgestrel-only products from the U.S. Food and Drug Administration.

- Interest in the progestin-only method was spurred with the 1998 publication of a multinational study showing it was more effective and resulted in less nausea and vomiting than the current combination regimen.
- Gynétics is familiar with the ECP territory because it introduced the Preven Emergency Contraceptive Kit in September 1998. The kit is now available by prescription in more than 25,000 U.S. drug stores.

RESOURCE

For more on the emergency contraception train the trainer program, contact:

Liz Callihan, Program Manager, Emergency Contraception Train-the-Trainer Program, Association of Reproductive Health Professionals, 2401 Pennsylvania Ave. NW, Suite 350, Washington, DC 20037. Telephone: (301) 320-8995. Fax: (202) 466-3826. E-mail: ecallihan@pubcomm.com.

product insert, general product information, and general emergency contraception information.

More providers are getting the message on emergency contraception. The Association for Reproductive Health Professionals (ARHP) in Washington, DC, for example, is sponsoring a train-the-trainer program this year on the subject. **(See box, above, for contact information.)**

This large-scale pilot program, supported by a grant from the David and Lucile Packard Foundation in Los Altos, CA, is designed to raise emergency contraception awareness among local and regional clinical communities across the U.S. Trained faculty specialties will include physicians, nurse practitioners, physician assistants, nurse-midwives, pharmacists, and other health care professionals from all 50 states. Program partners include the Planned Parenthood Federation of America in New York City and the Reproductive Health Technologies Project in Washington, DC.

An expert advisory committee has developed a thorough program curriculum and is providing a core faculty of health care providers from every state with the tools to speak in a variety of venues, says **Wayne Shields**, ARHP president.

"This program is based on the assumption that learning is contextual and that an effective clinical training program addresses the realities of everyday life for American women and their health care providers," Shields states. "The curriculum offers core clinical essentials, alternative approaches, and information about related issues such as the legal environment and the media."

The Family Planning Association of Maine in Augusta used a grant from the John Merck Fund in Boston to provide training and education to physicians and midlevel providers in rural Maine on the uses, availability, and appropriateness of ECPs. Between 1996 and 1998, more than 500 providers received EC education, says **Evelyn Kieltyka**, head of program services.

The evaluation component of the project called for 2,389 anonymous surveys to be mailed in August 1996 to an assortment of physicians, nurse practitioners, and nurse-midwives, Kieltyka says. Eleven percent of them were returned. The same survey was mailed in June 1998, with a return rate of 23% — almost double the rate of the initial survey, she notes.

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Set clear guidelines for Norplant removals

What is your clinic's policy when it comes to Norplant removals upon patient request, particularly when it comes to costs? Be sure that you understand that policy and share it with your patient during the counseling session before selecting the method.

Why is it so important to have such a policy? A recently published study of Norplant users found that although the majority of women perceived no provider or cost barriers to removal, one-third reported at least one factor. The most common barrier was the perception that cost would make it more difficult to remove Norplant.[1]

EXECUTIVE SUMMARY

A recently published study of Norplant users found that while the majority of women perceived no provider or cost barriers to removal, one-third reported at least one factor. The most common barrier was the perception that cost would make it more difficult to remove Norplant.

- Providers need to counsel women about the management and tolerance of side effects in a manner that communicates an openness to removal.
- Clinics must ensure that if a woman wants her Norplant implants removed, her request must be honored.

Norplant has high continuation rates in comparison with other methods, and the majority of users are satisfied with the implant contraceptive, says **Deborah Kalmuss**, PhD, associate professor in the Center for Population and Family Health at Columbia University in New York City and one of the investigators on the multicenter trial. Many women who have had implants in place for five years are returning to clinics for reinsertions, she notes.

Providers walk a fine line in counseling Norplant users, Kalmuss observes. They need to counsel women about the management and tolerance of side effects in a manner that communicates an openness to removal.

Perceptions of barriers

Kalmuss and colleagues examined the experiences of 687 low-income women who chose Norplant implants. Researchers gathered information through interviews before insertion, six months after insertion, and two years after insertion or at the point of discontinuation.

Although 64% of women in the study perceived no barriers to Norplant removal, 20% of respondents said their health care provider tried to convince them to continue using Norplant, and 9% felt pressured to stay on the method. All participants were enrolled in clinics that offered free Norplant removal, but 11% still assumed they would incur the cost of the procedure, while 18% indicated the cost would make it more difficult to get the implant removed.

Did any of these perceived barriers block removal? None of the anticipated barriers stopped women from initiating a removal discussion with their providers, and only one of the four proposed barriers — cost — had an effect on the removal decision.

Cost no barrier

Removal of implants must be done regardless of a patient's ability to pay, state the authors of *Contraceptive Technology*.[2] This agreement must be honored, even if the implants were not originally inserted by the provider.

"Clinics must ensure that no woman using Norplant ever has a problem in having the implants removed, no matter where inserted," concurs **Allan Rosenfield**, MD, dean of the school of public health at Columbia University in New York City.

Although the removal procedure requires staff time and effort, ways must be found to provide the service, even to those who are not eligible for Medicaid or Title X reimbursement, notes Rosenfield, who chaired a committee on contraceptive research and development at the Institute of Medicine in Washington, DC. The committee convened a workshop to review the introduction and acceptance of Norplant implants.

Use Norplant resources

The Norplant Foundation provides financial assistance to women without insurance who cannot afford to pay for the Norplant system, its removal, or replacement. The Foundation is a nonprofit, independent organization, originally established with an unrestricted grant from Wyeth-Ayerst Laboratories of Philadelphia, manufacturer of the implant system. **(For contact information and other Norplant resources, see box, below.)**

The company also has established a provider network to link women who desire implants or removals with trained personnel, says **Audrey Ashby**, a Wyeth-Ayerst spokeswoman. "We as a company believe that a woman should be able to have Norplant system inserted or removed at any time," she explains. In keeping with that policy, the company has sponsored training for more than 28,000 professionals in hands-on removal and insertion techniques and donated more than 20,000 system kits to health care professionals for use in eligible patients.

RESOURCES

Here are Norplant resource toll-free phone numbers:

(800) 934-5556. Patients should use this number to access the Norplant Health Care Professional Referral Network, a directory of providers trained in Norplant insertions and removals.

(800) 922-0877. Providers should call this number to access the Norplant Provider Support Center. The center offers telephone assistance Monday through Friday from 8 a.m.-8 p.m. EST.

(800) 760-9030. Patients can call this number to locate providers who are participating in the Norplant Foundation Supply and Removal Network. Information is available in English and Spanish.

To participate in the Norplant removal assistance network, or for more on reimbursement, contact:

The Norplant Foundation, P.O. Box 29240, Phoenix, AZ 85038-9986. Telephone: (800) 760-9030. Fax: (877) 855-5777.

Although the Norplant Foundation was set up to provide access to Norplant insertion, its role was expanded in 1995 to cover removal costs as well, says foundation chairman **Louise Tyrer**, MD, FACOG, of Incline Village, NV. Tyrer serves as medical director of the local Planned Parenthood and medical director for the Association of Reproductive Health Professionals in Washington, DC.

Providers must be trained in proper insertion and removal techniques before they are included in the national directory, Tyrer says. Nurse practitioners also are eligible for reimbursement, provided they have received proper insertion / removal training and are allowed through their state boards to receive such payment. The foundation recently enhanced its services for better data tracking and speedier provider reimbursement.

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Overcome barriers to correct condom use

Check the responses of the last three patients in your office when it comes to questions on condom use. Did you hear these answers? "Last time we used one, my partner took it off during sex because it was too uncomfortable." "The condom broke." "My boyfriend had one on, but he realized it was inside out and reversed it."

In most circumstances, family planning providers are offering double counseling. Not only are they talking directly to their female patients, they are providing information women can share with their partners about correct condom use. Although providers can offer female condoms, they also need to cover proper male condom use as well.

How do you address condom use in your counseling? If you start out with, "Do you use condoms every time you use sex?," you are liable to close the conversation before it has even started, suggests **Nicolas Sheon**, a PhD candidate in the University of California at Berkeley medical anthropology program and an HIV test counselor at the Berkeley Free Clinic. Sheon also serves as prevention editor of the University of California at San Francisco's *HIV InSite* Web site (http: / / hivinsite.ucsf.edu) and creator of www.managingdesire.org, an HIV prevention resource for medical providers, researchers, and laypersons.

Eliminate any judgmental air about condoms and give the patient a "safe space" to explain why condoms aren't used consistently or correctly, says Sheon. By opening with "When was the last time you used condoms?" you can start to assess where the patient is in condom use.

Follow up with some open-ended questions such as these:

- Have you had any problems with condoms feeling uncomfortable, breaking, or any other problem? Have any of your partners complained about using condoms?
- What was it specifically about condoms that you didn't like?
- Which partners do you use condoms with?

The responses will be in narrative form, rather than "yes" or "no," and you will begin to gather information about experiences, attitudes, and beliefs regarding condom use.

A recent study of condom use behaviors among male college students identifies common condom problems that result in a definite exposure to pregnancy and / or a sexually transmitted disease:[1]

- failure to start intercourse with a condom, then stopping to put it on;
- initiating intercourse with a condom, then removing it midway due to uncomfortable fit;

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Condoms need to be used correctly and consistently to provide effectiveness in preventing transmission of disease. Patients need good information, presented in a nonjudgmental manner, to help them use condoms with their partners.

- Provide a "safe space" to discuss condom use. Patients often are aware of the need to use condoms to prevent infection, but they often need more skills to become proficient condom users.
- Common condom problems include failure to start intercourse with a condom, then stopping to put it on; initiating intercourse with a condom, then removing it midway due to uncomfortable fit; breakage; slippage; and donning the condom inside out and reversing it during intercourse.

• breakage;
• slippage.

Patients need to understand that condoms must be put on — and kept on — throughout intercourse to obtain the protection afforded by the barrier device, says **Lee Warner**, MPH, the study's lead author and an epidemiologist with the Atlanta-based Centers for Disease Control and Prevention's Division of HIV / AIDS Prevention. **(See patient handout inserted in in this issue for facts about correct condom use.)**

Patients who report frequent breaks may benefit from larger condoms and use of water-based lubricants. For those who note that the condom "fell off," remind them of the need to hold the rim of the condom at the base of the penis and withdraw soon after ejaculation.

Experience plays a large role when it comes to condom problems. An international study recently reported on approximately 130 male condom users who were given five condoms for vaginal intercourse over a three-week period. Those with a history of one or more condoms that broke or slipped off reported about twice as many condom failures as those not in this at-risk group.

These data suggest that a history of condom failure predicts future failure, a finding that may be useful for targeted intervention.[2]

Tips for condom use

Condom counseling involves a type of salesmanship, Sheon reflects. Not only is the counselor offering the advantages and benefits of condom use, but he or she is helping the patient learn the same techniques to use with partners.

Assess the patient's comfort level in discussing and demonstrating condom use. Sheon likes to open two sizes of condoms, then blow a little bit of air into them so patients can see the shape. Put condoms of different thickness on the table so patients can touch them to feel the difference.

Give patients trial sizes of water-based lubricants to take home along with their condoms. All of these techniques will help spark interest in condoms and help patients leave with a more open view toward using them in the future.

"I think it is really important for people to leave with the message that maybe the condom they used didn't work because they weren't using a good quality condom, or there's a better condom out there," says Sheon. "They shouldn't give up on condoms completely." **(Learn how communities are getting the word out about condom use in the next issue of *Contraceptive Technology Update*.)**

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Community approach gets a grip on syphilis

Cases of primary and secondary syphilis are at their lowest levels in the United States since reporting began in 1941.[1] If that statistic leaves you complacent, then take a tip from public health officials in Guilford County, NC: Never lose your vigilance, because the outbreak in an outlying area may be at your doorstep the next day.

Syphilis is manifested increasingly as an epidemic rather than an endemic disease in the United States; focal outbreaks are still occurring. That message was driven home to workers at the Greensboro-based health department when an increase in syphilis cases from neighboring Forsyth County soon manifested as a sharp uptick in cases in Guilford County.

In 1996 and 1997, 153 cases of primary and secondary syphilis were reported each year in

EXECUTIVE SUMMARY

Syphilis is at its lowest level since reporting began in the United States, yet focal outbreaks continue.

- A multidimensional approach taken by local, state, and national public health officials helped turn the tide against one such outbreak in Guilford County, NC. Community-based organizations played a key role in getting the word out on syphilis detection and prevention.
- Rapid testing in local correctional facilities helped identify and treat several syphilis cases. Jails and hospital emergency departments have been identified as sites of high prevalence during epidemics because many arrested persons lack medical insurance or used emergency department services at their last medical visit.

Guilford County, representing a 147% increase from the 62 cases reported in 1994.[2] A concerted effort among Guilford County health officials and community resources took a fast-track, broad-based approach to tackling the problem.

Along with help from the North Carolina Division of Epidemiology in Raleigh and the Centers for Disease Control and Prevention (CDC) in Atlanta, the group effort appears to have paid off. Based on reported cases of primary and secondary syphilis in Guilford County through August 1998, cases are expected to decrease 38% in 1998 from 1997.

"We have projected that there will be a significant decrease for the end of 1998," reports **Madeline Sutton**, MD, MPH, a CDC epidemic intelligence service officer. "After instituting some of the interventions that came out of their community outreach effort and CDC's part of the investigation and later initiatives that followed, it looks like they [Guilford County] were able to have an impact."

Increase in cases not surprising

Use of crack cocaine and exchange of sex for drugs are fuel for a syphilis outbreak.[3] Because Guilford County is intersected by two major highways, it is not surprising that syphilis should flare up, explains **Harold Gabel**, MD, MPH, director of the county health department. When the increase was identified, local officials swiftly moved into place. Calling in state and national health resources, the county pulled representatives from a broad cross-section of community groups into what was dubbed the "War Room."

"We began to sit down and figure out how to get on top of this thing," reports Gabel. "It was a fairly intense process with a table with about 20 people sitting around it from all different places: CDC assignees, state people, community-based organization people, our own staff, health educators, and STD investigators."

Participants fanned out across the county to spread the news about the plan to combat syphilis. Gabel went to county OB/GYNS to ask that women be tested at delivery in addition to the first and third trimesters. He also let local internists know that if they suspect syphilis in a patient, they should call the health department for immediate testing. Judges were asked to be particularly vigilant with people arrested for prostitution or drugs in terms of urging them to get tested for syphilis.

Officials formed Rapid Intervention Outreach Teams to educate the community about syphilis, notes Sutton. Members spent two or three days doing active research, such as drawing blood, to detect more cases. Public health officials worked closely with law enforcement to offer earlier testing within the correctional facilities. While full testing was being performed some 10 to 14 days after incarceration, many inmates were moving out before testing was provided.

"We now have people going into the jails at least twice a week for education and testing," Gabel says. "We all have constraints in terms of money, space, and time, and jails aren't medical units, but they have really tried hard to make the testing as available as possible and to set space aside and to do it as frequently as possible."

Guilford health officials participated in a recent regional sheriffs' conference to update law enforcement officers from the 11 surrounding counties on syphilis, he says. Jails and hospital emergency departments have been identified as sites of high syphilis prevalence during epidemics, since many arrested persons lack medical insurance or used emergency department services at their last medical visit.[4] By targeting these areas, public health officials can make an impact on syphilis in areas with endemic or epidemic syphilis.

Public perceptions of local health departments are not always good ones, notes Gabel. Guilford public officials were concerned at first that many citizens would not want to come to the health department for screening. Thanks to the efforts of the local organizations who participated in the syphilis outreach program, the department now has increased acceptance in the community.

"The community organizations which went out into neighborhoods had credibility because they were either associated with the communities or had entrees," he says. "By doing street outreach, they not only got into these neighborhoods, but they built up our credibility."

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Mid-Years
WOMEN'S HEALTH

Using biochemical bone markers in osteoporosis

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Osteoporosis or osteopenia is a significant health problem, estimated to affect 23 million women in the United States. Each of these women is at risk for fracture and the potentially devastating associated consequences.[1,2] Recently, several important advances in identifying, treating, and managing osteoporosis have occurred.

Osteopenia and osteoporosis can be identified readily using bone mineral densitometry (BMD) measurement. New pharmacologic treatments, such as alendronate (Fosamax, manufactured by Merck & Co. of Whitehouse Station, NJ) and raloxifene (Evista, manufactured by Eli Lilly and Co. of Indianapolis), have been approved for preventing and/or treating osteoporosis.[1,3] In addition to those advances, serum and urinary bone markers have been found valuable in evaluating treatment efforts in women with osteoporosis and predicting bone loss among postmenopausal women.[4-6]

Managing osteoporosis requires a holistic approach, providng education about exercise and calcium intake, identifying those at risk, measuring bone density, prescribing appropriate pharmacologic agents, and evaluating treatment. This column will describe serum and urinary bone markers and their use for evaluating treatment and risk for bone loss. Biochemical markers of bone formation and resorption are produced during bone remodeling processes. Remodeling begins with osteoclast digestion of the bone surface, which creates an erosion cavity. These cavities are filled by osteoblasts, which migrate to the surface of the bone, synthesize, and secrete bone matrix proteins, which consist mostly of type I collagen.

Next, a modified form of the lysine amino acid forms crosslinks between the newly formed collagen and previously existing mature collagen. These crosslinks enhance the mechanical strength of the new collagen surface. Noncollagen proteins, consisting mostly of osteocalcin, make up the rest of the protein matrix. After the protein matrix is formed, calcium salts mineralize the surface over a one- to two-week period.

Resorption and formation processes produce byproducts measurable in urine or serum. Resorption occurs when osteoclasts digest bone collagen. This breakdown of the lysine crosslinks produces byproducts, which are released into the bloodstream and excreted directly through the urine.

The levels of these byproducts, including plasma tartrate-resistant acid phosphatase and urinary hydroxyproline, pyridinoline, deoxypyridinoline, and N-teleopeptide crosslinks, rise in relation to bone resorption activity.[3-5] Likewise, byproducts of bone formation increase as bone formation increases. Osteoblasts synthesize the new protein matrix and release osteocalcin, bone-specific alkaline phosphatase, and pro-collagen I extension peptides into the bloodstream.[3-5]

Urinary crosslinks are used most often to assess bone resorption. Several urinary crosslinks can be measured, including pyridinoline (found in type I and II collagen), deoxypyridoline (found only in type I collagen), and N-teleopeptide (highly specific to type I collagen). Of these, the crosslinked N-teleopeptides (NTx) are most commonly evaluated. NTx is measured by enzyme-linked immunoassay (ELISA) using the Osteomark assay. This assay requires a first- or second-morning void specimen (prior to 10 am) and preferably fasting. The cost of the Osteomark assay varies depending on the laboratory, but is generally about $50.[4] Normal (premenopausal) NTx levels in women range from 5-65 nmol/L BCE/mol/L creatinine.[6]

In 1995, the Food and Drug Administration (FDA) approved urine immunoassays of bone markers for use in clinical practice for osteoporosis.[4,7] A compact, portable dipstick machine, similar to home blood glucose monitoring devices, likely will be available in the near future for office measurement of urinary NTx levels.[8]

Osteocalcin is the biochemical marker most frequently used to evaluate bone formation. Levels are measured using serum radioimmunoassay; fasting morning specimens are generally preferred. Normal serum osteocalcin levels in postmenopausal women range from 1.5-11.0 ng/ml.[6] Osteocalcin levels often are used in research on osteoporosis, and FDA approval for use monitoring osteoporosis treatment is expected soon.[4]

Because bone markers give an indication of bone remodeling process rates but do not give specific data regarding actual bone mass,[7] they are used with BMD measurement. Actual bone mass is determined using BMD, and baseline NTx is evaluated. Repeat NTx measurements are determined in three to six months with a decrease of 30% to 60% (indicating reduced resorption) indicating treatment effectiveness.[4,6] Likewise, decreases in osteocalcin levels indicate slowing of bone formation, which signals a decrease in bone turnover and stabilizing of remodeling processes.

Bone markers were identified as valuable for predicting bone loss among postmenopausal women in a large multicenter trial. NTx levels below 38 predicted no bone loss in the next year, but, levels between 49 and 64 predicted losses of 1.5%, and levels over 64 predicted losses of 2.5% over the next year.[6] When BMD is unavailable, due to rural location, or difficult to interpret, due to fracture or degenerative changes, NTx can aid in determining response to treatment and estimating rates of bone loss. These biochemical markers offer a cost-effective method of evaluating treatment without waiting to reassess BMD. Not all insurers cover bone marker measurements, so coverage consideration should be weighed before use.

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Providers who missed the recent women's conference, "Blending Traditions in the 21st Century: A Women's Health Symposium," have a second opportunity to attend the event Sept. 29-Oct. 1 at Marco Island, FL. The symposium is cosponsored by the National Association of Nurse Practitioners in Reproductive Health (NANPRH) and the American College of Nurse-Midwives, both based in Washington, DC. A wide range of

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