25th Anniversary

CONTRACEPTIVE TECHNOLOGY UPDATE

A Monthly Newsletter for Health Professionals

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

FEBRUARY 2005
VOL. 26, NO. 2 • (pages 17-28)

Be prepared to counsel on use of DMPA and bone health issues

New labeling warns prolonged drug use may result in bone density loss

It's time to update your counseling on the injectable contraceptive depot medroxyprogesterone acetate (DMPA, Depo-Provera, Pfizer; New York City). The Food and Drug Administration (FDA) has added a "black box" warning to the drug's labeling to highlight that prolonged use may result in the loss of bone mineral density (BMD).

The new label states that bone loss in women who use Depo-Provera is greater with increased duration of use and may not be completely reversible. The injectable contraceptive should be used as a long-term birth control method (longer than two years) only if other birth control methods are inadequate, the label advises. Women who continue to use Depo-Provera past the two-year mark should have their BMD evaluated, according to the new labeling.

Since Depo-Provera was approved for U.S. use in 1992, its prescribing information has included a warning that use of the product may be considered among the risk factors for development of osteoporosis. Two

EXECUTIVE SUMMARY

The Food and Drug Administration has added a "black box" warning to the labeling for the injectable contraceptive Depo-Provera (depot medroxyprogesterone acetate or DMPA, Pfizer, New York City) to highlight that prolonged use may result in the loss of bone mineral density.

- The new label states that bone loss in women who use Depo-Provera is greater with increased duration of use and may not be completely reversible.
- The injectable contraceptive should be used as a long-term birth control method (longer than two years) only if other birth control methods are inadequate, the label advises.

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

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Subscription rates: U.S.A., one year (12 issues), $449. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. **Back issues**, when available, are $75 each.(GST registration number R128870672.) **Photocopying:** No part of this newsletter may be reproduced in any form or incorporated into any information retrieval system without the written permission of the copyright owner. For reprint permission, please contact Thomson American Health Consultants. Address: P.O. Box 740056, Atlanta, GA 30374. Telephone: (800) 688-2421. World Wide Web: http://www.ahcpub.com.

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Statement of financial disclosure: **Dr. Hatcher** (editorial board chairman and peer reviewer) discloses that he is a consultant for Pharmacia Corp., performs research for Ortho, and is on the speaker's bureau for Ortho, Wyeth, Organon, Berlex, and Pharmacia Corp. **Dr. Kaunitz** (board member) discloses that he does continuing medical education presentations and publications for Aventis, Organon, Ortho-McNeil, Pharmacia Corp., and Wyeth-Ayerst, is a consultant for Aventis, Barr Laboratories, Berlex, Johnson & Johnson, Lilly, and Pharmacia Corp., and is a stockholder in Aventis and Johnson & Johnson, and performs research for Barr Laboratories, Berlex, Galen, Lilly, Merck, National Institutes of Health, Organon, Parke Davis, Pfizer, Pharmacia Corp., R.W. Johnson Pharmaceutical Research Institute, and Solvay. **Ms. Dominguez** (board member) discloses that she is on the speaker's bureau for Ortho, Pfizer, Roche, and Organon. **Ms. Wysocki** (board member) discloses that she is on the speaker's bureau for Ortho-McNeil, Wyeth Ayerst Pharmaceuticals, Berlex, Organon, Pharmacia Corp., Pfizer, and Bristol Myers Squibb. **Dr. Nelson** (board member) serves on the speaker's bureau for Berlex Laboratories, Gynetics, Eli Lilly & Co., 3M Pharmaceuticals, Ortho-McNeill, Organon, Parke-Davis, Pfizer, Pharmacia Corp., and Wyeth Ayerst; she conducts research for Ortho-McNeil, Pfizer, and Pharmacia Corp. **Dr. Rosenfield** (board member) is a stockholder and board member of Biotechnology General Corp., a consultant for Organon; serves on the speaker's bureau for Organon, Wyeth-Ayerst, and Parke-Davis; and conducts research for Organon, Wyeth-Ayerst, Ortho-McNeil, and Parke-Davis.

This publication does not receive commercial support.

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studies, one enrolling women ages 25-35 and the other aimed at adolescents, were begun in the mid-1990s to clarify the drug's impact on BMD. Results from the studies, which have not yet been published, provide the background for the drug's revised labeling.

According to Pfizer, the new research indicates that a decrease in BMD appears to be at least partially reversible in adults and adolescents when the use of Depo-Provera is discontinued. A study to assess the reversibility of loss of BMD in adolescents is ongoing.[1]

Pfizer and the FDA decided to add the warning following review of the two studies, states **Christine Parker**, FDA spokeswoman. According to Parker, both studies were seven-year, prospective, nonrandomized surveillance studies designed to evaluate bone mineral density changes.

Pfizer has issued a revised patient information sheet for the drug and distributed a "Dear Health Care Practitioner" letter to alert potential and existing prescribers of the new labeling. **(See the resource box on p. 19 to get web access to these and other pertinent documents, as well as Pfizer telephone contact numbers for clinicians and patients.)**

Will warning affect use?

According to an FDA talk paper issued on the new labeling, black box warnings are used "to highlight special problems, particularly those that are serious, and to give health care professionals a clear understanding of a potential medical complication associated with a drug."[2] Family planning clinicians are familiar with such warnings; combined oral contraceptives carry a black box warning to alert that cigarette smoking increases the risk of serious cardiovascular side effects from Pill use.

Seeing such a warning on the contraceptive injectable label may seem scary for some clinicians and patients, says **Andrew Kaunitz**, MD, professor and assistant chair in the Obstetrics and Gynecology Department at the University of Florida Health Science Center/Jacksonville. Understanding that reaction is a new reality with the use of Depo-Provera for contraception, he adds.

However, concerns about BMD should not prevent use of DMPA in any appropriate user, states Kaunitz, who will present results from the adult DMPA study at the annual clinical

meeting of the Washington, DC-based American College of Obstetricians and Gynecologists May 7-11. **(Check upcoming issues of *Contraceptive Technology Update* for further reports on those data.)**

Review earlier research

Clinicians have eyed DMPA's potential impact on bone health since the 1990s, when initial research determined that women using DMPA had bone density values intermediate between those of normal premenopausal and postmenopausal women.[3] A subsequent study of some of the original DMPA users who discontinued the method found that bone density tended to increase after the method was stopped.[4]

A more recent investigation indicates that women using the injectable for two years recorded an approximate 6% decline in bone mineral density, compared with a loss of 2.6% among women on oral contraceptives.[5] **(Read more about this research in the *CTU* article, "Latest research sheds new light on DMPA's impact on bone health,"October 2004, p. 109.)**

Further research indicates that DMPA may be used on a long-term basis without fear of linear bone loss leading to early osteoporosis. Scientists who conducted a small study in China followed women for three years.[6] They found the annual rate of bone loss at three sites was significantly less than projected values, and the duration of DMPA use was not significantly related with the rate of bone loss. **(*CTU* reviewed the research in its article, "Bone mineral density and DMPA: reassuring news," April 2001, p. 41.)** Results from two cross-sectional studies indicate that DMPA's effect on BMD is small and reversible.[7,8]

Adding back estrogen may be effective in mediating the effects of DMPA; results from a 2003 published study show that when DMPA users were given a daily dose of 0.625 mg conjugated estrogens, no loss of BMD was seen.[9]

What about use of DMPA in adolescents? The contraceptive injection has become a popular choice for teens, who have come to rely on its convenience. Many family planners ascribe the drop in teen pregnancy in the United States in the 1990s to use of such contraceptives as DMPA and the contraceptive six-rod implant Norplant.[10]

According to Pfizer, it is unknown if use of Depo-Provera during adolescence or early adulthood will reduce peak bone mass and increase the risk of osteoporotic fracture in later life. Half of a woman's bone mass is gained during puberty and the first several years after menarche; peak bone mass is achieved in the early to mid-20s.[11]

The new concern raised by the FDA addresses bone loss in adolescent women, comments **David Archer**, MD, professor of obstetrics and gynecology and director of the Clinical Research Center at the Eastern Virginia Medical Center in Norfolk. This bone loss is believed to be due to the low estradiol levels in these women during the use of DMPA, he notes.

"Clinicians should be aware of this issue and use discretion in terms of the duration of DMPA use in young [under age 16] women," states Archer.

How about calcium supplementation? While there is no research to point to whether adequate calcium use can mitigate the bone loss with DMPA injections, all women and teens should be encouraged to take calcium supplementation, as well as have adequate magnesium and vitamin D intake in their diets, says **Sharon Schnare**, RN, FNP, CNM, MSN, clinician at South Kitsap Family Care Clinic, Port Orchard, WA. **(For a**

RESOURCES

- **To review the updated material on Depo-Provera**, visit the Pfizer corporate web page, www.pfizer.com, Click on "News," then under "News Release Archive," click on "2004." Click on the date "November 18, 2004." A copy of the press release is available for on-line reading as well as links to the "Dear Healthcare Professional" and "Dear Healthcare Organization Leader" letters, full prescribing information, and patient product information.
- **Clinicians with questions about Depo-Provera** should contact Pfizer's medical information line. Dial (800) 438-1985 and select option 6. Medical information is available Monday through Friday, 8:30 a.m. to 6 p.m., Eastern Time. Patients should call the Depo-Provera Contraceptive Injection patient support line at (866) 554-3376.
- The Washington, DC-based **U.S. Agency for International Development (USAID) has issued a helpful technical bulletin on the DMPA labeling change**. To review the bulletin, visit the agency's Maximizing Access and Quality (MAQ) Initiative web site, www.maqweb.org, and click on the link "Technical Update: USAID/W Technical Assessment of Recent Evidence on Depo-Provera and Bone Density."

patient handout on calcium and osteoporosis available in Spanish and English, see *CTU*, September 2001, insert.)

Clinicians will want to review the new Depo-Provera labeling with patients who are considering DMPA use. Include a discussion of other contraceptive options with women who have any of the following risk factors for osteoporosis:

- metabolic bone disease;
- chronic alcohol and/or tobacco use;
- anorexia nervosa;
- strong family history of osteoporosis;
- chronic use of drugs that can reduce bone mass, such as anticonvulsants or corticosteroids.

How about women who have been successful with DMPA use and wish to continue past two years with the method? Consider adding back estrogen, whether in postmenopausal doses of 0.625 mg conjugated estrogen in pill or transdermal form, or 1 mg estradiol in pill form, suggests Kaunitz. The estrogen dose in such postmenopausal therapies will be effective, even though they are much lower than that encountered with combined oral contraceptives, he adds.

How about using a time-out period after two years of DMPA use to mitigate any possible impact on bone?

"We have not had the opportunity to review any data on dosing regimens that incorporate periodic time off from using DMPA; therefore, we cannot comment on the potential benefit of such a dosing regimen in order to reduce the decrease in bone mineral density that is likely to be associated with the long-term use of DMPA," says Parker.

It is too early to say what recommendations will emerge regarding complete cessation or time off from DMPA, states **Susan Wysocki**, RNC, NP, president and CEO of the Washington, DC-based National Association of Nurse Practitioners in Women's Health.

"There will probably be some recommendations that come out about switching to other methods on a periodic basis," she observes. "There is no hard-and-fast rule."

References

1. Pfizer. Pfizer statement regarding additional prescribing information for Depo-Provera. Press release. Nov. 17, 2004. Accessed at: www.pfizer.com/are/news_releases/2004pr/mn_2004_1118.html.
2. Food and Drug Administration. Black box warning added concerning long-term use of Depo-Provera contraceptive injection. Nov. 17, 2004. Accessed at: www.fda.gov/bbs/topics/ANSWERS/2004/ANS01325.html.
3. Cundy T, Evans M, Roberts H, et al. Bone density in women receiving depot medroxyprogesterone acetate for contraception. *BMJ* 1991; 303:13-16.
4. Cundy T, Cornish J, Evans MC, et al. Recovery of bone density in women who stop using medroxyprogesterone acetate. *BMJ* 1994; 308:247-248.
5. Berenson AB, Breitkopf CR, Grady JJ, et al. Effects of hormonal contraception on bone mineral density after 24 months of use. *Obstet Gynecol* 2004; 103(5 Pt 1):899-906.
6. Tang OS, Tang G, Yip P, et al. Further evaluation on long-term depot-medroxyprogesterone acetate use and bone mineral density: A longitudinal cohort study. *Contraception* 62:161-164.
7. Orr-Walker BJ, Evans MC, Ames RW, et al. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal postmenopausal women. *Clin Endocrinol (Oxf)* 1998; 49:615-618.
8. Petitti DB, Piaggio G, Mehta S, et al. Steroid hormone contraception and bone mineral density: A cross-sectional study in an international population. *Obstet Gynecol* 2000; 95:736-744.
9. Cundy T, Ames R, Horne A, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *Clin Endocrinol Metab* 2003; 88:78-81.
10. Brindis C. Building for the future: adolescent pregnancy prevention. *J Am Med Womens Assoc* 1999; 54:129-132.
11. DMPA and bone density loss: An update. *Contraception Report* 1999; 10(5). Accessed at www.contraceptiononline.org/contrareport/article01.cfm?art=86. ■

Hormonal-based male contraceptive moves ahead

Clinical trials expected to start this year

Clinical trials for a male contraceptive that is a combination of progesterone and testosterone are expected to begin this year.

The study is being conducted by the Bethesda, MD-based National Institute of Child Health and Human Development of the National Institutes of Health, reports **Diana Blithe**, PhD, program director. The research will be conducted at two clinical sites: one headed by Christina Wang, MD, at Harbor-University of California, Los Angeles Medical Center in Torrance, and the other headed by William Bremner, MD, PhD, at the University of Washington in Seattle. The test product is a combination of two gels, testosterone gel and Nestorone gel, with the latter to be prepared and supplied by the New York City-based Population Council.

While surveys show men are very interested in having a male contraceptive and might prefer an oral contraceptive, the problem is that hormonal-based contraceptives can cause

EXECUTIVE SUMMARY

Clinical trials are expected to begin in 2005 in the United States for a male contraceptive that combines two gels: one comprised of testosterone and the other of Nesterone.

- Hormonal approaches, such as this one, impact testosterone production in the testes to reduce sperm production and then provide serum testosterone to prevent feminization.
- While surveys show men are very interested in having a male contraceptive and might prefer an oral contraceptive, the problem is that hormonal-based contraceptives can cause unpleasant side effects. Researchers are looking at different options to minimize such effects.

unpleasant side effects, experts say.[1]

Male contraceptive researchers note that the same side effects have posed problems for female contraceptives as well. Researcher **Deborah O'Brien**, PhD, associate professor at the University of North Carolina School of Medicine in Chapel Hill, says, "The concerns some of us have are the same as for hormonal contraceptives for women. They're systemic and so are likely to have side effects elsewhere, and that's true with any hormonal contraception."

For example, if a hormonal contraceptive shuts down on testosterone production, there likely will be feminization side effects, which are not very desirable and acceptable to men, says **Michael Rosenberg**, MD, MPH, clinical professor of obstetrics/gynecology and epidemiology at the University of North Carolina-Chapel Hill and president of Health Decisions in Chapel Hill..

"The real issue is the ability to do the testing on these contraceptives well enough and quickly enough to refine the products and take them through the testing stage pretty quickly," he says.

They will take a lot of refinement and require balancing, he notes. "Look at female contraceptives and how hormonal balance has been handled," Rosenberg notes.

The advantage to hormonal contraceptive approaches is that these types are the furthest along in the male contraceptive pipeline, says Blithe.

Hormonal contraceptives were the first to make it to clinical trials, including etonogestrel in implant form and testosterone undecanoate in injection form, which have had Phase II trials in Europe. And a Phase III trial of injectable testosterone undecanoate was conducted by the Geneva-based World Health Organization last year in China. **(See "Is male contraceptive on horizon? Trials under way" in the April 2004 issue of *Contraceptive Technology Update*, pp. 42-44.)**

Most hormonal approaches impact testosterone production in the testes to reduce sperm production and then provide serum testosterone to prevent feminization, so other body functions will be normal, but the man will not produce sperm, Blithe says.

NIH conference featured latest research

The Future of Male Contraception conference, sponsored by NIH, and held Sept. 29-Oct. 2, 2004, featured a variety of lectures and poster abstracts about hormonal approaches. For example, one new study tested 22 healthy young men who received eight weeks of combined testosterone and levonorgestrel treatment to augment gonadotropin and intratesticular androgen withdrawal with the goal of providing greater spermatogenic suppression.[2]

The treatment significantly decreased intratesticular androgens from baseline.[2]

Other new research discovered that nonsteroidal selective androgen receptor modulators provide a potential alternative for testosterone replacement therapies, including hormonal male contraception.[3]

"There are very intriguing sets of research done so far," Rosenberg says. "The problem is being able to provide contraception without impairing other things that are important, like secondary sex characteristics and like passing the blood-testes barrier. You want a drug to act in the testes, but not anywhere else."

Since male contraceptives are so early in development, it's difficult to say what ultimately will work best, but it appears that safety issues will be the biggest hurdles, Rosenberg says.

"The ability of a male contraceptive to increase a person's desire and not diminish his performance and eliminate worry about pregnancy would be very desirable," he says. "There's a real parallel with the development of female contraceptives. It's been in refining the safety."

References

1. Weston GC, Schlipalius ML, Bhuinneain MN, et al. Will Australian men use male hormonal contraception? A survey of a postpartum population. *Med J Aust* 2002; 176:208-210.

2. Matthiesson KL, Stanton PG, Amory JK, et al. Effects of testosterone and levonorgestrel combined with a 5-alpha reductase inhibitor or long-acting GnRH-antagonist on

serum and intratesticular reproductive hormone profiles. Presented at the *Future of Male Contraception* conference. Seattle; Sept. 29-Oct. 2, 2004.

3. Chen J, Hwang DJ, Miller DD, et al. An orally bioavailable selective androgen receptor modulator (SARM) for hormonal male contraception. Presented at the *Future of Male Contraception* conference. Seattle; Sept. 29-Oct. 2, 2004. ■

Male contraceptives are gaining momentum

Methods hold potential for greater safety

The first male contraceptives to make it to the market likely will be hormonal-based birth control, similar to what has worked well for female contraceptives for the past four decades. However, there are serious difficulties with hormonal contraceptives for men, so the possibilities that are beginning to excite researchers working in the contraceptive field are the nonhormonal methods.

"We have to consider all of the possibilities," says **Deborah O'Brien**, PhD, an associate professor at the University of North Carolina School of Medicine in the department of cell and developmental biology in Chapel Hill.

There is a need for a variety of contraceptive options for men and women, she says. "Nonhormonal and post-testicular methods are what we're shooting for," she says. "We'd like to inhibit sperm specifically and not have side effects elsewhere."

O'Brien has been working on a contraceptive target involving novel sperm glycolytic enzymes.[1]

"There are two potential advantages of this kind of approach," O'Brien says. "One is they're expressed only in germ cells, and two, enzymes are considered [potential] drugs by the pharmaceutical industry."

The hypothesis is that glycolysis is required for sperm motility and male fertility; so if a drug could inhibit glycolytic enzymes necessary for the production of sperm, then fertility would be compromised.[1]

"We have good evidence from studies that if we can eliminate one of the sperm-specific enzymes then sperm are infertile," O'Brien says. "We've proved proof of principle that it will work; it's been done in mice."

O'Brien's investigations have shown that the germ cell-specific isozyme, glyceraldehyde 3-phosphate dehydrogenase-S can be eliminated, resulting in sperm having no forward motility.[1]

"Researchers have a good idea of how you would go about designing inhibitors and other kinds of interactions — like protein interactions also are potential targets — but we don't have drugs yet that work that way," O'Brien says. "We can conceive of ways to inhibit it, but it's not like having an enzyme or [other products] already targeted in the pharmaceutical industry."

The bad news is that it will take a while to get from this proof of principle to actual male contraceptive drugs, O'Brien notes.

Another potential target for nonhormonal male contraceptives involves ion channels, which control the excitability of cells.

In 2001, Boston investigators discovered an ion channel, named CatSper for cation channel of sperm that was located only in mature sperm in the tail.[2]

"It was no where else in the body, and it didn't get put into cell membranes by cells until the sperm were mature," says **David E. Clapham**, MD, PhD, one of the investigators and an Aldo R. Castaneda professor of cardiovascular research and an investigator at the Howard Hughes Medical Institute and professor of neurobiology at Harvard Medical School and the Children's Hospital of Boston.

CatSper discovered accidentally

Clapham discovered CatSper by accident since he primarily works in cardiology and neurobiology. When he and co-investigators discovered the ion channel, they tracked it down to discover what it did and found that it was only present in sperm, which seemed to make it an obvious

EXECUTIVE SUMMARY

Researchers are exploring a variety of novel, nonhormonal male birth control methods as an alternative to hormonal contraceptives and their potential side effects.

- One possible contraceptive target involves novel sperm glycolytic enzymes.
- Another possibility involves CatSpers, which are ion channels that are located only in mature sperm in the tail.
- The advantage to a drug targeting CatSper is that it potentially would work only on the sperm cells and would have no long-term effect on reproduction.

novel target for a contraceptive, he recalls.

"When we knocked out the ion channel in mice, the gene that encoded it, the mice were completely infertile," he recalls. "Then we studied the mice sperm and found they had a small defect in motility, but they're mainly unable to hyperactivate, which is required for fertilization."

Hyperactivation gives sperm greater force that is needed to penetrate the protective cells around an egg and then penetrate the egg, Clapham points out.

Researchers hypothesize that CatSpers bring calcium into the sperm and that they are used to initiate movement and change of movement of the tail, he says.

"So the significance for contraception is that ion channels are good targets for drugs because they're on the surface of cells," Clapham explains. "Since this channel is only present in mature sperm, if you blocked it specifically, it would not have effects on any other tissues."

As a specific blocker, the contraceptive would work only on cells that potentially would die or fertilize, so it would have no long-term effect on a man's reproduction, he adds.

A biotechnology company named Hydra of Cambridge, MA, has licensed this potential target and is working on trying to develop a small molecule blocker of CatSper, Clapham says.

Comparable pharmaceutical solutions are the calcium channel-blocking drugs that are used to treat hypertension, he notes.

"The analogy here would be to find a small molecule that would block only this calcium channel and not any others, and that should block hyperactivation," Clapham explains.

While hormonal contraceptives for men are the furthest along in development, they are not as promising an approach for the long term, he says.

"I think that's an unlikely approach because I don't think many men will take a hormone that will affect their fertility for unknown duration and which has other side effects," Clapham says. "You have to worry if it's going to be reversible and make sure it doesn't affect your offspring."

All contraceptives have to have a very high safety margin because they're used for changing a lifestyle and not for treating a disease, and so the approaches that are more likely to affect sperm formation in the long term are riskier, he says.

While research into male contraceptives is a positive development, there already are two male contraceptives that are cheap, safe, and effective, but they've been underutilized in the 100 years that they've been available: condoms and vasectomy, says **Robert Hatcher**, MD, MPH, senior author of *Contraceptive Technology*, and professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta. He is the chairman of the editorial advisory board for *Contraceptive Technologies Update*.

"In the world today, there are only four nations, the Netherlands, Bhutan, New Zealand, and Great Britain, where more men get vasectomies than women get tubal sterilization in spite of the fact that vasectomy is less expensive, safer, and is the most effective contraceptive of all, and it can be verified with semen analysis," Hatcher says. Condoms have pretty good effectiveness against many sexually transmitted diseases and are very effective against HIV, for example, and they are the only means of preventing infections if you have high-risk couples, Hatcher says. "But what contribution is this method making in the world today?" he says. "In many locations, [it is] minimal, and in some societies, moderate, but in no place is it excellent."

Given the history of men not using condoms and vasectomy as much as they could, Hatcher says he doesn't see much potential for the new male contraceptives.

References

1. O'Brien DA. Novel sperm glycolytic enzymes as contraceptive targets. Presented at the *Future of Male Contraception* conference. Seattle; Sept. 29-Oct. 2, 2004.

2. Clapham DE. The CatSper family of sperm-specific ion channels. Presented at the *Future of Male Contraception* conference. Seattle; Sept. 29-Oct. 2, 2004. ■

Clinical trials begin for spray-on contraceptive

Phase I trial enrolls six women

A spray-on birth control method for women recently has entered a Phase I clinical trial in which six women in Sydney, Australia, are using the new product as part of a study to determine whether the transdermal contraceptive can be used in spray formulation effectively.

Named Nestorone Metered Dose Transdermal System, the fourth-generation progestin is being studied through a joint development agreement between the Population Council of New York City and Acrux, a pharmaceutical company of

EXECUTIVE SUMMARY

A Phase I clinical trial is under way for Nestorone Metered Dose Transdermal System (MDTS), a fourth generation progestin, and investigators are studying the spray-on contraceptive in six women in Sydney, Australia.

- Nestorone has strong progestational activity and antiovulatory potency, and it's expected to have few side effects.
- The spray-on drug is being studied through a joint development agreement between the Population Council and Acrux, a Melbourne, Australia pharmaceutical company.
- The contraceptive delivery system is placed gently against the skin and depressed, which releases a light spray that quickly dries on the skin.

Melbourne, Australia. FemPharm, a wholly owned subsidiary of Acrux, is the study's sponsor.

Nestorone has strong progestational activity and antiovulatory potency, but it has no androgenic or estrogenic activity in vivo, which makes it suitable for contraception use.[1] Since it is very potent, it can be delivered via long-term delivery systems, such as vaginal rings, implants, and transdermal system.[1]

"This is only a beginning of clinical trials to see if Nestorone could be used in spray formulation to deliver the Nestorone progestin in sufficient amounts to be effective," says **Regine Sitruk-Ware**, MD, executive director of product research and development for the Center for Biomedical Research at the Population Council in New York City.

"The Phase I trial under way is also to define how the hormone behaves in the circulating blood," she reports.

The trial involves six postmenopausal, healthy women because investigators don't want to interfere with the cycle of ovulatory women at this early stage in which they are studying the kinetics of the product, Sitruk-Ware adds.

The contraceptive works this way: The delivery system is placed gently against the skin and depressed, which releases a light spray that quickly dries on the skin, she explains.

Then the delivery system uses an enhancer, which is patented, and the rapid drying formulation of the drug and enhancer on the skin effectively form a reservoir within the skin from which the drug slowly is absorbed into the circulation over time, Sitruk-Ware says.

"The drug is filled into a glass bottle and closed with a manual pump-metering valve," Sitruk-Ware adds. "A once-a-day application typically delivers consistent amounts through the skin to the blood stream."

No dropouts or adverse events were reported among the six volunteers as of the end of December. The trial will be completed in the first quarter of 2005, reports **Sushma Kumar**, PhD, senior clinical research associate with the Center for Biomedical Research at the Population Council.

The next clinical trial will be designed based on the results from this one, and the location of the new trial has not yet been determined, she says.

So far, none of the nestorone containing contraceptives has reached the market, although several new delivery systems have made it to market. "Many clinical trials using vaginal rings, implants, and gel have been completed in 2,000 women," Kumar explains.

Nestorone has been found to be safe in clinical trials, she notes. For example, vaginal rings used to deliver contraceptive hormones, such as nestorone, have shown few side effects and good control of menstrual bleeding.[2] The possible side effects are typical of hormonal contraceptive methods and include headache, acne, dizziness, depression, nervousness, breast soreness, nausea, and bleeding/spotting, she notes.

"Although we have not observed any local side effects, there may be possible skin irritation at the site where the Nestorone is sprayed," Kumar says.

A direct comparison of spray-on administration could be made with transdermal patches, she adds.

"Although about 5% to 10% of the subjects using transdermal patches can experience skin irritation due to the fact that the skin is covered with an occlusive system for seven days, with this technology, no such irritation was observed in the earlier clinical trials using similar formulations," Kumar says.

The cost of spray-on administration has not been determined, but nestorone is not expensive and the system can be refilled with canisters, so the cost of the system is a one-time cost with additional costs only when the canister is changed each month, Kumar and Sitruk-Ware say.

A spray-on birth control method provides yet another possible solution to the world's need for different contraceptive options for women and couples in developed and developing countries, they add.

"The greater the number of options, the higher the probability that users will find a convenient method that suits their needs and will be compliant with it," Sitruk-Ware says.

While it's too early to run acceptability studies for the contraceptive spray, a large acceptability study in several countries is warranted, she notes.

The advantage of this mode of delivery is related to the nonoral administration of steroids and also to the fact that it is not visible as a patch, Sitruk-Ware adds.

"As compared to the gel, it is not sticky and dries very quickly," she says. "Studies conducted previously with Nestorone gel in Latin America were very successful, and women liked this method."[3,4,5]

References

1. Sitruk-Ware R, Small M, Kumar N, et al. Nestorone: Clinical applications for contraception and HRT. *Steroids* 2003; 68:907-913.

2. Johansson ED, Sitruk-Ware R. New delivery systems in contraception: Vaginal rings. *Am J Obstet Gynecol* 2004; 190(4 Suppl):S54-9.

3. Jordan A. Toxicology of progestogens of implantable contraceptives for women. *Contraception* 2002; 65:3-8.

4. Massai MR, Diaz S, Quinteros E, et al. Contraceptive efficacy and clinical performance of Nestorone implants in postpartum women. *Contraception* 2001; 64:369-376.

5. Harwood B, Mishell DR. Contraceptive vaginal rings. *Semin Reprod Med* 2001; 19:381-390. ■

African American women hit hard by HIV/AIDS

Rates are 19 times higher than white women

African American women are far more likely to be infected with HIV than are white women and Hispanic women, a problem that has been growing, according to recent reports by the Centers for Disease Control and Prevention (CDC).

Non-Hispanic black females have 19 times the rate of HIV infection as non-Hispanic white females and five times the rate as Hispanic women, according to surveillance data from 32 states between 2000 and 2003.[1]

In all, 28% of the HIV/AIDS cases diagnosed in the 32 states from 2000 to 2003 were of women; and of these cases, about 69% were African American women. CDC surveillance data counted 25,254 HIV/AIDS diagnoses among African American women, compared with 6,545 cases among white women and 3,792 cases among Hispanic women.[1]

EXECUTIVE SUMMARY

The HIV/AIDS epidemic continues to disproportionately affect women of color, with African American women 19 times more likely to be infected than white women, according to recently released data from the Centers for Disease Control and Prevention (CDC).

- Non-Hispanic black females have five times the rate of HIV infection as Hispanic women.
- About 80% of the African American women who have been diagnosed with HIV/AIDS in 2000-2003 were infected through high-risk heterosexual contact.
- The CDC spent $49 million on prevention services, predominantly for racial and ethnic minorities, in early 2004.

"When you look at the HIV/AIDS rates, the rates were higher among minorities since the beginning, but the numbers didn't [ratchet up] until the mid-'90s, and since then it's been predominantly a racial minority epidemic," says **Robert Janssen**, MD, director of the CDC's Division of HIV/AIDS Prevention-Surveillance and Epidemiology.

The HIV epidemic among African Americans is fueled by socioeconomic factors, including poverty and lack of access to health care and preventive services as well as stigma and discrimination, reports **Allan Rosenfield**, MD, dean of the Mailman School of Public Health at Columbia University in New York City.

Drug use by women or their partners also contributes to the epidemic, he says.

There need to be better educational efforts aimed at this population, as well as continued use of needle exchange programs and easier access to the health care system, Rosenfield adds.

Too many unanswered questions

Historical data show that most of the earlier HIV/AIDS cases were among African American women involved in injection drug use (IDU), but now most are infected as a result of heterosexual sex, Janssen says.

In targeting prevention programs for African American women, there are obstacles due to unanswered questions, he notes.

"We don't know the women's partners," Janssen says. "For example, are their partners men who are injection drug users and were infected that way and then infect their women partners sexually, or are

their partners men who also have sex with men?"

CDC data show that 80.4% of the African American women diagnosed with HIV/AIDS in 2000-2003 were infected through high-risk heterosexual contact, while 16.7% were infected through IDU. For white women, 67.1% were infected through high-risk heterosexual contact, and 30.4% were infected through IDU. Among Hispanic women, the IDU group was 17.9%, and the high-risk heterosexual contact group was 78.7%.[1]

While researchers have studied the possibility that some women are infected with HIV after having high-risk sex with men who have been incarcerated, this does not appear to be a major cause of transmission, Janssen says. "There's a lot more sex going on in the communities than in jail. What's been known for a while is people who are HIV positive are among the groups being at high risk for imprisonment as well."[2,3]

The CDC spent $49 million in early 2004 to provide prevention services predominantly for racial and ethnic minorities, Janssen says.

"We wanted to be sure we were getting services to high-risk people and not only men who have sex with men (MSM), which is a very important population, but also African American women, who are important, as well," he explains. "The grants are written in a way that there's preferential funding for targeting one of those populations."

Testing and counseling is a good entry point for prevention services because it identifies people whose behavior places them at risk for HIV and diagnoses people who don't know they're infected, Janssen notes. "Testing and counseling presents an opportunity to get people into the appropriate prevention services," he adds.

According to a CDC data and the National Health Interview Survey in the United States in 2002, most HIV tests (43.5%) conducted among persons ages 18-64 occurred in private doctor offices. Hospitals, including outpatient clinics and emergency departments, accounted for 22.4% of HIV tests. However, AIDS clinics had conducted only 5.2% of the tests, while community health clinics accounted for 3%, STD clinics only 0.1%, and family planning clinics conducted 1.6% of the HIV tests.[4]

The CDC reported that greater percentages of pregnant women (about half) and of persons at increased risk for HIV (about one-quarter) had been tested during the preceding 12 months than were other persons.[4] The latest CDC guidelines promote routine HIV testing of all pregnant women and advise health care providers to include HIV testing, when indicated, as part of routine medical care on a voluntary basis, similar to how other diagnostic and screening tests are offered.[5]

References

1. Diagnoses of HIV/AIDS — 32 states, 2000-2003. *MMWR* 2004; 53:1,106-1,110.
2. Lane SD, Rubinstein RA, Keefe RH, et al. Structural violence and racial disparity in HIV transmission. *J Health Care Poor Underserved* 2004; 15:319-335.
3. Clark JG, Stein MD, Hanna L, et al. Active and former injection drug users report of HIV risk behaviors during periods of incarceration. *Subst Abus* 2001; 22:209-216.
4. Number of persons tested for HIV — United States, 2002. *MMWR* 2004; 53:1,110-1,113.
5. Advancing HIV prevention: New strategies for a changing epidemic — United States, 2003. *MMWR* 2003; 52:329-332. ■

Letter to the Editor

Top 25 events might have included these items

To the Editors of *Contraceptive Technology Update*:

I have been a subscriber to *Contraceptive Technology Update* for many years and rarely take issue with the content. I must, however, register my total surprise and dismay at your "25 Events to Know in Reproductive Health" that appeared in the January 2005 issue. Two of the most glaring that were omitted, from a national and international health perspective, are:

1. Introduction and development of suction curettage in the 1950s coupled with the development manual vacuum aspiration using the Karmen cannula (soft tip). These were epic events that changed the lives of millions of women forever. They made induced abortion safer and remain the foundation for abortion services in the United States and throughout the world. In support of this, please see the following quote taken from a recent presentation by **Malcolm Potts**, published by the British Pregnancy Advisory Service: *Abortion Law Reforms: Pioneers of Change.*

Professor Potts, MB, Bchir, PhD, is a former member and executive committee member of the Abortion Law Reform Association and a professor of Population and Family Planning at the University of California, Berkeley, and is the former president of Family Health International.

"Shortly after the [abortion] law was reformed [in England], I met an American called Harvey Karmen [PhD], who had gone one step further than the Eastern Europeans in simplifying early abortion techniques (sharp curettage). He had devised a plastic 50 ml syringe with a flexible plastic cannula that made it possible to do abortions with a piece of equipment costing only a few pounds. Harvey and I published the first description in *The Lancet* in 1972, and since that time the technology has gone round the world. "

2. Introduction of the Yoon falope ring for laparoscopic tubal ligation in the late 1960s by, I believe, Drs. In Bae Yoon and Theodore King in an article published in *AJOB/GYN* or *Obstetrics and Gynecology*.

I trust you will not think my response "overly picky." The battle for reproductive health rights and services has been a long and difficult one. Tragically, in all too many instances, the medical community, especially eminent obstetricians and gynecologists, has obstructed progress. Karmen, went to jail because of his beliefs and experience, which subsequently were confirmed one-thousandfold. He clearly deserves a prominent place in the history of reproductive health.

The work of Yoon should not be overlooked either. Voluntary sterilization remains the contraceptive method with the greatest impact on population stabilization nationally and globally. The development of the Yoon falope ring revolutionized ambulatory voluntary sterilization-made it safer, easier to do, dramatically shorter recovery period and reversible. It still remains a major factor in the continuing efforts to limit population growth.

— **Noel McIntosh**, MD, ScD, Senior Associate, Population and Family Health Services, Bloomberg School of Public Health, Johns Hopkins University in Baltimore, and Adjunct Professor of International Health at Tulane University School of Public Health, New Orleans

Dear Dr. McIntosh:

Thank you for your very insightful letter. You might be interested to know that suction curettage, a far safer approach to therapeutic abortions than sharp curettage, was described in the 1920s at Johns Hopkins. Papal pronouncements in 1930 and 1931 terminated terminations in your fair city immediately. The turn of suction abortions and the role of the Karmen cannula in therapeutic abortions and menstrual regulation procedures worldwide has led to safer, more widely available abortions in most countries worldwide.

You are right! This was an omission from our list. We stand corrected. Dr. Potts and his wife, Martha Campbell, PhD, have pointed out to me that abortion is readily available in all 60 nations that have achieved a stable population. . . . all, that is, except Ireland, where women can and do obtain abortions readily in England or on ships that set anchor off the coast of Ireland!

As you know, tubal sterilization is the most commonly used method of birth control throughout the world (as well as in the United States). The role of the falope ring has been immense, so you are right again!

We thank you and ask any other readers who would like to send us their comments, to do so.

— **Robert Hatcher**, MD, MPH, *CTU* Editorial Advisory Board Chairman ■

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 **June 2005** 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. ■

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 "**Be prepared to counsel on use of DMPA and bone health issues.")**
- **Describe** how those issues affect service delivery and note the benefits or problems created in patient care in the participant's practice area. (See **"Hormonal-based male contraceptive moves ahead"** and **"Clinical trials begin for spray-on contraceptive.")**
- **Cite** practical solutions to problems and integrate information into daily practices, according to advice from nationally recognized family planning experts. (See **"African American women hit hard by HIV/AIDS.")**

5. According to new labeling for Depo-Provera Contraceptive Injection, a woman should only continue to use the drug for what period of time if other birth control methods are inadequate for her?

A. Longer than five years
B. Longer than three years
C. Longer than two years
D. Longer than one year

6. What is one of the major challenges to bringing a hormonal-based male contraceptive to market?

A. Finding a way to destroy sperm
B. Finding the right hormonal balance to minimize side effects, such as feminization
C. Passing a proof-of-principle test
D. Producing the contraceptive in a pill instead of an injection

7. A new spray-on contraceptive called the Nestorone MDTS works in which way?

A. Twice a day, a woman will spray a metered amount of Nestorone MDTS on the inside of her thighs.
B. The delivery system sprays a metered amount of the contraceptive on a woman's lower belly, which she lets dry for a count of 60 before dressing herself.
C. Once a day, the delivery system is placed gently against the skin and depressed releasing a light spray, which quickly dries on the skin and forms a reservoir within the skin from which the drug is slowly absorbed into the circulation over a period of time.
D. The once-a-day spray delivers a dose of progesterone and estrogen that impacts ovulation for 12 hours at a time.

8. The CDC has made what recommendation regarding HIV testing of women?

A. All women should be offered an HIV test at their first gynecological exam.
B. Pregnant women should be routinely tested for HIV, and health care providers should screen routinely for HIV whenever it is indicated.
C. All African American women should be offered an HIV test at annual medical checkups.
D. All women who are about to deliver a baby should be given an HIV test.

Answers: 5. C; 6. B; 7. C; 8. B.

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.*

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