25th Anniversary

CONTRACEPTIVE TECHNOLOGY UPDATE

A Monthly Newsletter for Health Professionals

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

JANUARY 2005
VOL. 26, NO. 1 • (pages 1-16)

Look to the future for bold changes in reproductive health

Microbicides and male contraceptives soon may be added to the list

(Editor's note: This issue of Contraceptive Technology Update *marks the 25th anniversary of the newsletter. In this issue, you'll see observations from reproductive health experts, reviews of important research, and a timeline of reproductive health events. We hope you enjoy this special edition of* CTU.*)*

Look ahead five to 10 years, and you may see a male contraceptive on the market, as well as a microbicide for women that offers contraception as well as female-controlled protection against HIV and other sexually transmitted diseases (STDs), say reproductive health experts.

Researchers are examining different approaches to identifying molecules controlling spermatogenesis and oocyte maturation, sperm-egg fusion, and endometrial implantation of the early embryo. By applying genomics and proteomics technology or building upon genetic analysis of model organisms, scientists hope to unlock new discoveries that will lead to more

Bulletin: FDA issues approvable status for single-rod contraceptive implant

American women are one step closer to having a contraceptive implant option with the recent Food and Drug Administration (FDA) issuance of approvable status for Implanon, the single-rod contraceptive implant from Organon (West Orange, NJ).

According to the FDA, an approvable letter signals that the agency is prepared to approve the product dependent on the company meeting specified conditions.

Organon is in the process of meeting those requests, states

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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.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (ahc.customerservice@thomson.com). Hours of operation: 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday, EST.

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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contraceptive options.[1]

"The future will be very much influenced by new pharmaceutical agents," forecasts **Leon Speroff**, MD, associate director of the Women's Health Research Unit at Oregon Health & Science University in Portland. "The knowledge gained from molecular biology allows the development of drugs that will target specific tissues and functions, minimizing unwanted effects."

New methods of contraception must be made available if the challenge of unmet need is to be effectively addressed. According to a recent Washington, DC-based Institute of Medicine publication, more than a quarter of pregnancies worldwide are unintended. Between 1995 and 2000, nearly 700,000 women died and many more experienced illness, injury, and disability as a result of unintended pregnancy.[2]

"Our biggest current problem is maternal morbidity and mortality around the world due to a lack of acceptance of post-ovulatory methods of contraception," states **David Archer**, MD, professor of obstetrics and gynecology and director of the Clinical Research Center at the Eastern Virginia Medical Center in Norfolk. "We need to address this issue directly; reducing maternal mortality should be our key message."

Zeroing in on men

One of the greatest family planning achievements in the past 25 years has been the acceptance by the majority of U.S. women of the use of oral steroidal contraception, reports Archer. Women's acceptance of hormonal contraception is a tacit understanding of the need to limit family size and most importantly, the safety of the method, he notes.

But when it comes to contraception for men, similar progress has not yet been achieved. According to results of a 2000 survey, men are interested, with most favoring a pill, but many signaling acceptance of an implant or injection.[3]

Progress may be forthcoming, says **Régine Sitruk-Ware**, MD, executive director for product research and development at the Center for Biomedical Research at the New York City-based Population Council, a nonprofit research organization. The Population Council is actively researching male contraceptive methods, says Sitruk-Ware, who participated in "Reproductive Health in the Twenty-First Century," an October 2004 conference sponsored by the Cambridge, MA-based Harvard University's Radcliffe

Institute for Advanced Study. The Population Council is researching use of its trademarked synthetic androgen, 7-alpha-methyl-19-nortestosterone (MENT) as a possible male contraceptive. Scientists are studying use of the androgen since it suppresses gonadotropin secretion, which leads to suppression of testosterone and sperm production in the testes. ***(Contraceptive Technology Update* reviewed such contraceptive research in its January 2004 article, "Male contraceptives: Research examines options," p. 6.)**

Pharmaceutical companies Schering AG of Berlin and Organon International of Oss, The Netherlands, are jointly investigating a hormonal method of contraception for men. Scientists are looking at a gestagen implant and a testosterone injection in Phase II trials.

Just-published research indicates that male immunocontraception may be a viable option.[4] Scientists injected Eppin, a testis/epididymis-specific protein, in male monkeys, making them infertile. When the injections were stopped, the monkeys regained their fertility status. Such early research may provide an avenue for larger scale examinations.

Focus on benefits

Expect to see more contraceptive methods with noncontraceptive benefits, says Sitruk-Ware. The levonorgestrel intrauterine system (Mirena IUS, Berlex Laboratories, Montville, NJ), which was developed by the Population Council, is being examined for potential use in treating menorrhagia.[5] ***(CTU* reported on the research in the June 2004 article, "Research eyes IUS use for menstrual bleeding," p. 67.)**

"The trend is that the contraceptive should bring added medical benefits in order to have more compliance with the system by the user, with more desire to use it and more support by the community," she states.

Pills will continue to represent an important contraceptive choice for women. New information presented at the 2004 annual meeting of the American Society for Reproductive Medicine highlighting the long-term noncontraceptive benefits of oral contraceptives (OCs) provides good news regarding OC safety, observes **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center/Jacksonville.

The two presentations, based on Women's Health Initiative (WHI) data, indicated that among postmenopausal women, risks of cardiovascular disease and certain cancers were lower among those WHI participants who had previously used oral contraception compared with those who had not, states Kaunitz.[6,7]

According to Kaunitz, upcoming oral contraceptive

(Continued on page 6)

25 Events to Know in Reproductive Health

1950

Philanthropist Katherine McCormick and Planned Parenthood founder Margaret Sanger collaborate to promote **development of a physiologic contraceptive for women**. McCormick agrees to fund the work of Gregory Pincus, a Harvard University physiologist.

1951

Carl Djerassi, a chemist at Syntex, applies for a patent for the progestational agent known as **norethindrone**.

1953

Frank Colton, a chemist at GD Searle, applies for a patent for the progestational agent known as **norethynodrel**.

1954

Gregory Pincus and John Rock, professor of gynecology at Harvard Medical School, **first administer synthetic progestins to women**.

1956

First large **clinical trials of oral contraceptives begin** in Puerto Rico.

1957

The Food and Drug Administration (FDA) **approves norethindrone** (Norlutin; Syntex/Parke-Davis) and norethynodrel (Enovid; Searle) for "treatment of gynecologic disorders."

1958

Physician Lazar Margulies develops a plastic coil i**ntrauterine device (IUD)**.

1960

The FDA grants a contraception indication for **Enovid, which makes it the first approved oral contraceptive.**

1962

The Population Council organizes the **first international IUD conference;** physician Jack Lippes presents data on his loop IUD designed with a monofilament tail.

1969

The **first copper-bearing IUD** is described in medical literature by physician Jaime Zipper.

1971

The **Dalkon Shield IUD** is introduced in the United States.

1973

The U.S. Supreme Court **legalizes abortion nationwide with its ruling on *Roe v. Wade.***

1974

Marketing of the **Dalkon Shield is discontinued in the United States**.

1976

The **first progesterone-releasing IUD** is introduced in the United States.

1988

The **Copper T380A IUD is introduced** in the United States.

1990

The FDA approves **levonorgestrel subdermal implants (Norplant)**.

Bulletin

(Continued from cover)

Frances DeSena, company spokeswoman.

"Our next step is to provide FDA with the information they have requested so that we are can obtain approval," says DeSena. "Based on that approval, Organon plans to launch sometime in the first half of 2005."

Implanon is inserted under the skin of the upper arm, and provides contraception for up to three years. Consisting of a nonbiodegradable rod measuring 40 mm in length and 2 mm in diameter, the device releases the progestin etonogestrel at an average release rate of 40 mcg per day. Since the device does not contain estrogen, women who do not tolerate or are contraindicated to estrogen use may safely use it. ***(Contraceptive Technology Update* reported further details on Implanon in the December 2003 article, "Contraception forecasts: You'll have new options," and the October 2002 article, "Don't count implants out: 2 options may take Norplant's place," p. 109.)**

In a three-year study investigating the contraceptive efficacy and tolerability of Implanon, findings indicate that the device was well tolerated and had excellent, reversible, contraceptive efficacy.[1] Irregular bleeding was the primary reason for discontinuation (19%). Adverse events, other than bleeding irregularities, were generally mild to moderate in intensity and resulted in 9.3% of discontinuations.[1] The most commonly reported nonbleeding adverse events were breast pain (16%), acne (12.6%), vaginitis (12%), and pharyngitis (10.5%).[1] There is a rapid return to fertility in those women without fertility problems when the implant is discontinued.[2]

Bleeding disturbances are the main adverse events associated with implantable contraceptives.[3] Other minor risks relate to the insertion and removal procedures, which require adequately trained providers as well as aseptic techniques.[3] Provider education will be an important aspect of product introduction should Implanon receive FDA final approval. Organon is developing educational models on insertion and removal techniques to ensure clinicians are familiar and comfortable with the device.

"Organon is committed to conducting comprehensive training programs to ensure health care providers are instructed on the use of Implanon; we will also be providing education to consumers as well," states DeSena. Pending a decision from the FDA, the company will launch a web site and toll-free number for consumers and health care providers, she adds.

Option would be welcome

While 1 million to 2 million women in the United States currently use progestin-only injections (depot

medroxyprogesterone acetate or DMPA, Depo-Provera, Pfizer, New York City), progestin-only implant contraception options have been lacking since the 2000 removal of six-rod Norplant implant from U.S. pharmacy shelves. (Wyeth Pharmaceuticals, Madison, NJ, suspended shipment of implants in August 2000 when concerns arose about efficacy of suspect lots. While the lots were found effective in July 2002, the manufacturer chose not to reintroduce the product in the United States. **See the following *CTU* articles: "Check Norplant stock, company says: Recent batches might be ineffective," October 2000, p. 117; "Are Norplant's days numbered in the U.S.? Test results could decide its fate," November 2000, p. 129; and "Don't count implants out: 2 options may take Norplant's place," October 2002, p. 109.)**

"Implanon represents a great improvement over the six-capsule Norplant system," states **Anita Nelson**, MD, professor in the obstetrics and gynecology department at the University of California in Los Angeles (UCLA) and medical director of the women's health care clinic and nurse practitioner training program at Harbor-UCLA Medical Center in Torrance.

"It is a single-rod system with unsurpassed efficacy which is placed in less than one minute and can be removed in two to three minutes," she says.

Implanon is different from Norplant; it is longer and stiffer, due to its ethyl vinyl acetate composition, observes **David Archer**, MD, professor of obstetrics and gynecology and director of the Clinical Research Center at the Eastern Virginia Medical Center in Norfolk. Insertion and removal times are quicker since the system consists of one rod, he notes.

"We still receive calls from women interested in Norplant," states Archer, who serves on an advisory committee to Organon for physician training in implanting and removing the device. "There is a group of women who are interested in long-term progestin-only implants for contraception."

How will it work?

Three conditions must be met to ensure method success if Implanon is indeed released in the United States, says Nelson:

- Clinician training is imperative, not only for insertion and removal techniques, but for counseling as well.
- The side effects of the method need to be understood, especially the unpredictable spotting and bleeding.
- Women must have access to providers who are able to remove the implants upon their request.

Carrie Cwiak, MD, MPH, assistant professor of obstetrics and gynecology at Emory University in Atlanta, says, "I think one lesson we can learn from the Norplant experience is the importance of getting insertion and

1992

The injectable contraceptive **depot medroxyprogesterone acetate (DMPA, Depo-Provera)**, first tested in 1966, becomes available to U.S. women.

1993

U.S. regulatory approval is given to the **female condom.**

1996

The Filshie Clip is approved for use in tubal sterilization in the United States.

1997

The FDA approves use of certain brands of oral contraception for **emergency contraceptive use**.

2000

The FDA approves use of **mifepristone for use in medical abortion**.

The FDA approves **Mirena, the levonorgestrel intrauterine system**.

2001

The **Ortho Evra transdermal contraceptive patch** receives approval from the FDA.

2002

The **NuvaRing vaginal contraceptive ring** gains FDA approval.

2003

U.S. regulatory approval is given to **Seasonale, the first extended-regimen oral contraceptive**. ■

removal training before using Implanon clinically."

Implanon offers the options many women want in a contraceptive method: high efficacy and no need to adhere to a daily schedule for dosing, says **Linda Dominguez**, RNC, NP, assistant medical director of the Albuquerque-based Planned Parenthood of New Mexico.

"The three years of effectiveness matches the birth spacing rate that many women tell clinicians they are planning — 'maybe a baby in two or three years,'" she observes. "And many previous implant users have been waiting, with literally open arms, for this new product."

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3. Brache V, Faundes A, Alvarez F. Risk-benefit effects of implantable contraceptives in women. *Expert Opin Drug Saf* 2003; 2:321-332. ■

(Continued from page 3)

advances may include:

- new options for women interested in extended oral contraception, including continuous OC formulations;
- OC formulations with 24-25 active tablets per four-week cycle to enhance efficacy and cycle control;
- pills formulated with progestins new to the United States that may enhance safety, efficacy, and tolerability;
- OCs combined with folic acid to reduce the risk of birth defects when pregnancy occurs in the setting of current/recent OC use. **(Such a formulation is under review; see "FDA panel gives nod to adding folic acid to OC," *CTU*, March 2004, p. 28.)**

While significant progress has been made in the past 25 years when it comes to reproductive health, advocates will need to stay focused in helping to raise the status of women's health worldwide. Unmet need for family planning remains high in developing countries, despite the recent accelerated growth in the use of contraception, according to the Geneva-based World Health Organization. For example, in sub-Saharan Africa, an average of 23% of women of reproductive age who are married or in union are believed to need family planning services.[8]

In the United States, women await an FDA decision on sale of over-the-counter emergency contraception. In addition, state and federal legislative changes may impact current women's reproductive health choices. Two new editorials in family planning medical literature remind reproductive health clinicians of their need for advocacy for women's rights.[9,10]

Felicia Stewart, MD, adjunct professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California San Francisco and co-director of its Center for Reproductive Health Research & Policy, and co-author of one of the editorials, says, "The last four years have been hard on reproductive health — for women in the U.S. and around the world; the next four years will be, too, so it is helpful to have a sense of priorities for our attention."

Advocates need to make sure that all efforts address the concerns of women in a comprehensive way, since a narrow focus cannot gain the broad support needed to empower women's rights, she adds.

"Most of all, speaking up and not giving up are key; redoubled efforts are crucial if we hope to prevent further losses in funding and access to care," Stewart states.

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STDs: Research aims at 'hidden epidemic'

You suspect that your 17-year-old patient may have a chlamydia infection. Thanks to a nucleic acid amplification screen on a urine specimen, you are able to detect the sexually transmitted disease (STD) and report the results the next day.

Nucleic acid amplification tests (NAATs) that allow screening and diagnosis of such STDs as chlamydia and gonorrhea rank as top advances in the fight against these and other infections, say reproductive health experts.

"The introduction of nucleic acid amplification tests, specifically for chlamydia and gonorrhea, has provided incredible improvement in our ability to accurately diagnose these infections in a whole variety of populations, whether symptomatic or not," observes **Julius Schachter**, PhD, professor in the department of laboratory medicine at the University of California San Francisco (UCSF) and director of the UCSF Chlamydia Research Laboratory at San Francisco General Hospital Medical Center.

NAATs offer the ease of urine collection in men and women, with the added benefit of sensitivities and specificities similar to tests performed on urethral or endocervical samples.[1]

The impact of NAATs on test sensitivity and ease of sampling has been one of the most important advances in the past 25 years, says **Edward Hook III**, MD, professor of medicine and epidemiology at the University of Alabama at Birmingham and director of the STD control program for the Jefferson County (AL) Department of Health.

Similar diagnostic advances are needed if U.S. clinicians are to stem the spread of what has been termed "the hidden epidemic" of STDs.[2] An estimated 15 million cases of STDs occur in the United States each year.[3] On a global scale, the Geneva-based World Health Organization estimates there were 340 million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis in 1999, a sharp rise from the 250 million new cases in 1990.[4]

More than half of all new cases of STDs occur in young men and women younger the age of 25.[5] Reliable rapid-based tests need to be developed so clinicians can detect and treat such infections, says Schachter. **(Read more about this subject in the March 2004 *Contraceptive Technology Update* article, "Research eyes rapid testing of chlamydia," p. 31.)** Research indicates that as many as one-fourth of patients diagnosed with chlamydia never return for care,[6] he notes.

New test available

HIV detection has moved forward with the availability of an oral fluid-based test. The Food and Drug Administration (FDA) approved the use of oral fluid samples with the OraQuick Rapid HIV-1/2 Antibody Test (OraSure Technologies, Bethlehem, PA) in March 2004. The rapid HIV diagnostic test kit provides accurate screening in as little as 20 minutes. **(*CTU* reported on the approval in its June 2004 article, "FDA approves HIV oral fluid-based test," p. 64.)**

Look for the development of inexpensive, rapid, noninvasive, STD tests, such as chromatographic strip tests, that can be performed on site and that can identify a variety of STDs at the same time, says **Stuart Berman**, MD, chief of the epidemiology and surveillance branch in the Atlanta-based Centers for Disease Control and Prevention's (CDC) division of STD prevention.

Clinicians will have to stay a step ahead when it comes to stemming the spread of STDs. The CDC is alerting clinicians to be on the lookout for instances of lymphogranuloma venereum (LGV), an STD that occurs rarely in the United States, yet has recorded an uptick in the Netherlands, as well as Belgium, France, and Sweden.[7]

The infection is caused by a variant of the bacterium that causes chlamydia. Administering doxycycline 100 mg orally twice a day for 21

days may treat infection.[8]

According to the CDC, the most common clinical sign of LGV infection in heterosexual men is tender inguinal and/or femoral lymphadenopathy that is most commonly unilateral. Women and men who have sex with men may have proctocolitis or inflammatory involvement of perirectal or perianal lymphatic tissues.[8]

What's on tap?

Clinicians may see the commercial availability of a human papillomavirus (HPV) vaccine in the future, predicts **Ward Cates Jr.**, MD, MPH, president/chief executive officer of the Institute for Family Health at Family Health International, a Research Triangle Park, NC-based nonprofit research organization. Just-published research indicates a bivalent HPV vaccine is effective in prevention of incident and persistent cervical infections with HPV-16 and HPV-18.[9] The vaccine is under development by GlaxoSmithKline Biologicals in Rixensart, Belgium, as Cervarix.

Promising results also have been reported from trials of a vaccine developed by Merck & Co. of Whitehouse Station, NJ. Research presented at the November 2004 meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC, indicates that Merck's investigational monovalent vaccine against 16 (HPV 16) has 100% vaccine efficiency against cervical intraepithelial neoplasia at stages 2 to 3, confirming earlier published research.[10] ***(CTU* reported on the research in its February 2003 article, "HPV vaccine research yields promising results," p. 17.)** The vaccine is a component of Merck's investigational quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine.

Look for public health officials to combine genetic techniques and molecular biology to provide enhanced delineation of which individuals will be at risk for STDs, predicts Berman.

"We will be seeing a lot of work in the introduction of more effective intervention strategies, developing controlled efforts to reach and educate people" about STDs, agrees Schachter.

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25 years, 25 articles: Studies you should know

Research has been a cornerstone of contraceptive technology; the following noninclusive list includes 25 articles of note from the past 25 years.

Several selections are offered by **Deborah Kowal**, MA, adjunct assistant professor in the Rollins School of Public Health at Emory University in Atlanta, co-author of Contraceptive Technology, and the first editor for *Contraceptive Technology Update.* Kowal's presentation on top medical literature is a perennial favorite at the Contraceptive Technology conferences. The 2005 conferences are scheduled for March 9-12, 2005, in San Francisco and April 6-9, 2005, in Washington, DC. [More information is available at www. contemporary forums.com or by calling (800) 377-7707, or e-mailing info@cforums.com.]

ABORTION.

1. Beral V, Bull D, Doll R, et al. Breast cancer and abortion: Collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries. *Lancet* 2004; 363:1,007-1,016.

Data on women from 53 studies undertaken in 16 countries with liberal abortion laws were analyzed, with researchers concluding that pregnancies that end as a spontaneous or induced abortion do not increase a woman's risk of developing breast cancer.

CONTRACEPTION.

2. Audet MC, Moreau M, Koltun WD, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs. an oral contraceptive: A randomized controlled trial. *JAMA* 2001; 285:2,347-2,354.

Researchers designed an open-label, parallel-group trial, randomly assigning women to use of the transdermal contraceptive or an oral contraceptive (OC).

Findings indicate that the contraceptive patch is comparable to a combination OC in contraceptive efficacy and cycle control. Compliance was better with the weekly contraceptive patch than with the OC.

3. Roumen FJ, Apter D, Mulders TM, et al. Efficacy, tolerability, and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. *Hum Reprod* 2001; 16:469-475.

This yearlong, multicenter study assessed the contraceptive efficacy, cycle control, tolerability, and acceptability of the contraceptive vaginal ring. Findings indicate that the method is effective and well accepted.

DEPOT MEDROXYPROGESTERONE ACETATE (DMPA).

4. Strom BL, Berlin JA, Weber AL, et al. Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer. *Contraception* 2004; 69:353-360.

This study analyzed the relationship between breast cancer and use of injectable and implantable progestin-only contraceptives. Results indicate that progestin-only implants and injectables do not raise a woman's risk of breast cancer.

EMERGENCY CONTRACEPTION.

5. Von Hertzen H, Piaggio G, Ding J, et al. Low-dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; 360:1,803-1,810.

A randomized, double-blind trial in 10 countries showed that the three regimens studied are effective and prevent a high proportion of pregnancies if taken within five days of unprotected coitus. A 1.5 mg single levonorgestrel dose can substitute for two 0.75 mg doses 12 hours apart.

FAMILY PLANNING.

6. Arevalo M, Sinai I, Jennings V. A fixed formula to define the fertile window of the menstrual cycle as

What do you see as three of the most important reproductive health advances of the past 25 years?

"In the field of sexually transmitted diseases [STDs]: development of noninvasive STD testing methods (predicated upon molecular biologic techniques; development of syndromic management for STDs in some developing country settings; and development of transmission dynamics concepts, permitted in part by advances in mathematical modeling."

— Stuart Berman, MD, chief of the epidemiology and surveillance branch in the Atlanta-based Centers for Disease Control and Prevention's division of STD prevention

"The most important advances in the last 25 years in reproductive health include the development of and increasing access to mifepristone and medical abortion broadly; the broader range of delivery mechanisms for hormonal contraception, such as the patch, ring, and implants, and emergency contraception."

— **Kelly Blanchard**, president of Ibis Reproductive Health in Cambridge, MA

"I would suggest the three most important advances are the availability of medical abortion, the mainstreaming of emergency contraception, and the growth in condom use, especially by adolescents. If only technology, I'd pick the shift from dilation and curettage [D&C] to vacuum aspiration abortion."

— **Sharon Camp**, president of the Alan Guttmacher Institute in New York City

"In the field of sexually transmitted infections, the most important for diagnosis and treatment include polymerase chain reaction technology for easier screening, the development of acyclovir, and HIV antiretroviral drugs."

— **Ward Cates Jr.**, MD, MPH, president/chief executive officer of the Institute for Family Health at Family Health International in Research Triangle Park, NC

"Medical abortion, the levonorgestrel intrauterine system, and alternative delivery systems for contraceptive steroids, such as the patch, ring, and implant."

— **David Grimes**, MD, vice president of biomedical affairs at the Institute for Family Health at Family Health International in Research Triangle Park, NC

"Assisted reproductive technologies must rank very highly. It of course has created problems, but the amount of new knowledge gained will ultimately lead to progress with even better methods of contraception. Induced abortion by medical treatment is a tremendous step forward, especially in the developing world.

"The contribution to worldwide family health is enormous. It is very important that we have established the safety of estrogen-progestin contraception. The combined safety of lower doses and better patient screening by informed clinicians now makes serious side effects almost totally avoidable."

— **Leon Speroff**, MD, associate director of the Women's Health Research Unit at Oregon Health & Science University in Portland

the basis of a simple method of natural family planning. *Contraception* 2000; 60:357-360.

This article reports the results of an analysis of the application of a fixed formula to define the fertile window. By analyzing a large data set, researchers determined a fixed formula in which days 8-19 of the menstrual cycle are considered to be the fertile window. This research is the basis for the Standard Days Method.

7. Stewart FH, Harper CC, Ellertson CE, et al. Clinical breast and pelvic examination requirements for hormonal contraception: Current practice vs. evidence. *JAMA* 2001; 285:2,232-2,239.

After performing a review of current literature, the authors conclude that hormonal contraception can safely be provided based on careful review of medical history and blood pressure measurement. For most women, no further evaluation is necessary.

8. Trussell J, Hatcher RA, Cates Jr. W, et al. Contraceptive failure in the United States: An update. *Stud Fam Plann* 1990; 21:51-54.

This report updates the authors' previous estimates of first-year probabilities of contraceptive failure for all methods of contraception. Estimates are provided of failure during typical use (which includes incorrect and inconsistent use) and during perfect use (correct use at every act of intercourse). The difference between these two probabilities provides a measure of how forgiving of imperfect use each method is.

9. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995; 333:1,517-1,521.

A total of 221 healthy women, who were planning to become pregnant, stopped using birth-control methods and began collecting daily urine specimens and keeping daily records of whether they had sexual intercourse. Findings indicated that among healthy women trying to conceive, nearly all pregnancies can be attributed to intercourse during a six-day period ending on the day of ovulation.

10. World Health Organization (WHO). *Medical Eligibility Criteria for Contraceptive Use.* 3rd ed. Geneva; 2003.

The latest update of the WHO Medical Eligibility Criteria provides current guidance on provision of contraceptives.

HIV/AIDS.

11. Centers for Disease Control and Prevention. Pneumocystis pneumonia — Los Angeles. *MMWR* 1981; 30:250-252.

12. Centers for Disease Control and Prevention. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men — New York City and California. *MMWR* 1981; 30:305-308.

In 1981, clinical investigators in New York and California observed the first evidences of HIV/ AIDS infection in the United States: An unusual clustering of cases of rare diseases, notably Kaposi's sarcoma, and opportunistic infections such as *Pneumocystis carinii* pneumonia among young, previously healthy, homosexual men.

13. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus Type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994; 331: 1,173-1,180.

Scientists conducted a randomized, double-blind, placebo-controlled trial of the efficacy and safety of zidovudine in reducing the risk of maternal-infant HIV transmission.

In pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during the pregnancy, a regimen consisting of zidovudine given ante partum and intrapartum to the mother and to the newborn for six weeks reduced the risk of maternal-infant HIV transmission by approximately two-thirds.

HORMONE THERAPY.

14. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. *JAMA* 2003; 289:3,243-3,253.

The Women's Health Initiative trial of combined estrogen plus progestin was stopped early when overall health risks, including invasive breast cancer, exceeded benefits. Results from this analysis suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis.

15. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA* 2002; 288:49-57.

Investigators analyzed results from the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, blinded, placebo-controlled trial of 4.1 years' duration (HERS) and subsequent unblinded follow-up for 2.7 years. Researchers conclude that postmenopausal hormone therapy should not be used to reduce risk for coronary heart disease (CHD) events in women with CHD.

"Different ways of delivering hormones is one of the greatest steps forward. Now that we know more about their safety and health benefits, it is also wonderful to be able to offer hormonal methods like the patch, the ring, the intrauterine system, injections, and soon a new one-rod implant. These options give women greater flexibility to find the method that best meets their needs.

— **Susan Wysocki**, RNC, NP, president and chief executive officer, Association of Nurse Practitioners in Women's Health in Washington, DC

"The three things I see as most important are the lowering of the dose of ethinyl estradiol in combination hormonal contraception; the development of novel and more effective contraceptive options for women, such as the injectable, newer intrauterine devices, the patch, the vaginal ring, and Essure [transcervical sterilization]; and the development of mifepristone.

— **Edio Zampaglione**, MD, director of contraception at Organon Pharmaceuticals USA in Roseland, NJ

What three advances do you see in the next five to 10 years when it comes to contraception and reproductive health?

"Male contraception; new female-controlled HIV/STD prevention technologies; and freer access to contraceptives."

— Blanchard

"In the coming years, the biggest advances could be the emergence of safe and effective vaginal microbicides; the widespread availability of pre-natal genetic testing; and simple, reliable home tests for common STDs."
— Camp

"Over-the-counter availability of emergency contraception; availability of a single rod contraceptive implant, offering easier and faster insertion/removal than with multiple implant systems; and availability of lower-dose depot medroxyprogesterone acetate [DMPA] formulation administered by the subcutaneous route, which should facilitate DMPA self-administration."
— **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center/Jacksonville

"The three advances I see are development of highly effective nonsteroidal methods of contraception,(not barrier methods or locally applied gels/creams/films; development of a contraceptive that offers high efficacy along with sexually transmitted disease [STD] protection (unlike the condom); and development of a male contraceptive that is not coital-dependent.
— Zampaglione

16. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA* 2002; 288:58-66.

Further analysis of the HERS study data showed that treatment for 6.8 years with estrogen plus progestin in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery.

INTRAUTERINE DEVICES (IUDs).

17. Alvarez F, Brache V, Fernandez E, et al. New insights on the mode of action of intrauterine contraceptive devices in women. *Fertil Steril* 1988; 49:768-773.

To gain a better understanding of the mechanism of action of intrauterine devices, a search was made for ova in the genital tracts of 115 women using no contraception and of 56 women using IUDs, all of whom volunteered for study in conjunction with surgical sterilization.

Fertilized ova are less likely to reach the uterine cavity containing an IUD, researchers observed, thus leading them to conclude that the principal mode of IUDs is by a method other than destruction of live embryos.

18. Grigorieva V, Chen-Mok M, Tarasova M, et al. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. *Fertil Steril* 2003; 79:1,194-1,198.

Designed as a prospective before-and-after study of women with uterine leiomyomas who chose the levonorgestrel intrauterine system as their method of contraception, researchers found that the device was associated with a profound reduction in menstrual blood loss and may provide effective medical treatment of bleeding.

19. Hubacher D, Lara-Ricalde R, Taylor DJ, et al. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *N Engl J Med* 2001; 345:561-567.

This case-control study helps refute the myths that IUDs cause pelvic infection, increase ectopic pregnancy, and are inappropriate for young or never-pregnant women.

20. Lee NC, Rubin GL, Borucki R. The intrauterine device and pelvic inflammatory disease revisited: New results from the Women's Health Study. *Obstet Gynecol* 1988; 72:1-6.

Researchers analyzed data from the Women's Health Study, a hospital-based, case-control study carried out in the United States from 1976-1978, to examine whether the risk of pelvic inflammatory disease associated with IUD use varies with a woman's sexual behavior. Results indicated that women at low risk of acquiring sexually transmitted infections have little increase in the risk of pelvic inflammatory disease from use of an IUD.

OCs.

21. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med* 2002; 346:2,025-2,032.

Findings from this population-based, case-control study indicate that among women from 35 to 64 years of age, current or former OC use was not associated with a significantly increased risk of breast cancer.

22. Oral contraceptive use and the risk of ovarian cancer. The Centers for Disease Control Cancer and Steroid Hormone Study. *JAMA* 1983; 249:1,596-1,599.

The Centers for Disease Control and Prevention in Atlanta published this report as part of its Cancer and Steroid Hormone Study, a multicenter, case-control investigation. Researchers determined that the risk of ovarian cancer decreased with increasing duration of OC use and remained low long after cessation of use and estimated that more than 1,700 cases of ovarian cancer are averted each year by past and current OC use among American women.

23. The reduction in risk of ovarian cancer associated with oral-contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *N Engl J Med* 1987; 316:650-655.

Researchers used data from a case-control study, the Cancer and Steroid Hormone Study, to evaluate the reduction in risk of ovarian cancer associated with OC use. A protective effect was seen in women who had used OCs for as little as three to six months, and it continued for 15 years after use ended. It was independent of the specific OC formulation and of the histologic type of epithelial ovarian cancer. Findings indicate that the OC use decreases the risk of epithelial ovarian cancer.

24. Westhoff C, Kerns J, Morroni C, et al. Quick Start. A novel oral contraceptive initiation method. *Contraception* 2002; 66:141-145.

Investigators at an urban family planning clinic routinely offer patients starting contraceptive pills the option of taking the first tablet sooner. A telephone follow-up showed that women who swallowed the first OC in the clinic were more likely to continue the OC until the second package than women who planned to start the pills later.

STERILIZATION.

25. Peterson HB, Xia Z, Hughes JM, et al. The risk of pregnancy after tubal sterilization: Findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996; 174:1,161-1,168; discussion 1,168-1,170.

A multicenter, prospective cohort study was conducted in U.S. medical centers, with more than 10,000 women who underwent tubal sterilization followed for eight to 14 years.

The risk of pregnancy was assessed by cumulative life-table probabilities and proportional hazards models. Findings indicate although tubal sterilization is highly effective, the risk of sterilization failure is higher than generally reported. The risk persists for years after the procedure and varies by method of tubal occlusion and age. ■

GUEST COLUMN

Hormonal contraceptives: The future has arrived

By **Robert Hatcher**, MD, MPH
Professor of Gynecology and Obstetrics
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Atlanta

When the first combined oral contraceptive entered the marketplace in 1960, women began taking hormonally active pills for 21 days, followed by seven days of placebo pills, or no pills at all. This 21/7 regimen resulted in regular withdrawal bleeding every month.

Such regular monthly cycles are a modern phenomenon. Women in hunter-gatherer societies had 50 periods in a lifetime. In colonial times, women had about 150 periods. Today, women have 450-500 periods, due in part to the 21/7 regimen of combined hormonal contraception. However, extremely large studies have demonstrated that only 10%-15% of all cycles are exactly 28 days. Pills taken 21/7 change this!

The now-familiar pattern of very regular monthly withdrawal bleeds is now being changed. The introduction of progestin-only contraceptives such as depot medroxyprogesterone acetate (DMPA or Depo-Provera, Pfizer, New York City), Norplant implants (Wyeth, Philadelphia; no longer manufactured), and the levonorgestrel intrauterine system have resulted in long-acting contraception with scanty or no bleeding.

Extended-regimen contraception

We now have a dedicated extended-regimen contraceptive, Seasonale (Barr Pharmaceuticals, Woodcliff Lake, NJ) which results in four scheduled withdrawal bleeds a year. Providers are reporting that women are using the transdermal patch and the vaginal ring in an extended or continuous form, both resulting in altered forms of bleeding. **(See the box, right, for a list of contraceptive methods that lead to altered forms of bleeding.)**

A recent survey indicates 77% of providers are prescribing extended contraception.[1] I believe the future of hormonal contraception will be in the direction of the extended or continuous provision of hormones. This will result in patterns of bleeding that are completely different than the familiar regularity of scheduled withdrawal bleeds from pills taken 21/7. But the efficacy and safety of these new approaches will be comparable.

What is 'natural'?

Is it natural not to have periods? Providers often hear that question. Consider the history of prehistoric women, where "natural" meant pregnant, breast-feeding, and dead by age 50. Women prior to menarche and after menopause do not "store up" huge accumulations of endometrial tissue. Their endometrium (as is the case with women using pills continuously) is actually atrophic.

Women regularly experiencing inconvenience, messiness, blood loss, painful periods, cyclic migraines, and/or breast tenderness may be happier having periods less often or not at all.

Surveys tell us that many women, regardless of age, would prefer to eliminate menses completely or reduce their frequency to less than once a month.[2] Given the opportunity to determine how frequently they would menstruate, 44% of all women surveyed said they would prefer never to menstruate, and this number increases to 59% for women ages 40-49.[2]

Answer the questions

The use of hormonal contraception in extended or continuous forms has raised several questions, such as:

Methods that Lead to Irregular Bleeding/Amenorrhea

- Progestin-only pills
- Norplant (no longer available)
- Depot medroxyprogesterone acetate (DMPA)
- Extended use of birth control pills
- Extended use of the contraceptive patch
- Extended use of the contraceptive vaginal ring
- Levonorgestrel intrauterine system
- Single-rod contraceptive implant (approvable status)

• **Is it safe?**

Evidence from the one-year trial of extended use of Seasonale and the six-month trial of continuous use of a 20-mg ethinyl estradiol/100-mg levonorgestrel pill indicate no untoward effects on the endometrium.[3,4]

• **Will it affect return to fertility?**

Results from a German trial indicate a rapid return to fertility after discontinuation of an extended regimen.[5] Women who switched from the extended regimen to the conventional regimen experienced a rapid reversal of amenorrhea, and those who desired pregnancy conceived soon after discontinuation.[5]

The good and the bad

The advantages of extended regimens of contraception include convenience, increased ovulation suppression, and minimized cyclic symptoms. Such advantages come with drawbacks, as women need to be counseled on the initial irregular bleeding and the eventual amenorrhea that accompany extended regimens.

When combined oral contraceptives were first introduced, the regularity of the monthly withdrawal bleeds initially was seen as an important factor in women accepting the method. With new dosing regimens emerging, we are seeing more irregular bleeding patterns. Extended contraception options offer women and their clinicians important new contraceptive options.

References

1. Association of Reproductive Health Professionals and National Association of Nurse Practitioners in Women's Health. Annual meeting registrant survey. August-September 2002.

2. Association of Reproductive Health Professionals. Extended regimen oral contraceptives. *Harris Poll.* June 14-17, 2002.

3. Anderson FD, Hait H. Seasonale-301 Study Group. A multicenter, randomized study of an extended cycle oral contraceptive. *Contraception* 2003; 68:89-96.

4. Kwiecien M, Edelman A, Nichols MD, et al. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: A randomized trial. *Contraception* 2003; 67:9-13.

5. Wiegratz I, Hommel HH, Zimmermann T, et al. Attitude of German women and gynecologists towards long-cycle treatment with oral contraceptives. *Contraception* 2004; 69:37-42. ■

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. ■

COMING IN FUTURE MONTHS

- New progestins — what role do they play?
- Brush up your contraceptive counseling skills
- Getting it right — tips on taking patient history
- Research eyes extended regimens
- Tips on progestin-only methods

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 **"Look to the future for bold changes in reproductive health" and "Bulletin: FDA issues approvable status for single-rod implant.")**
- **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 contraceptives: The future has arrived.")**
- **Cite** practical solutions to problems and integrate information into daily practices, according to advice from nationally recognized family planning experts. (See **"STDs: Research aims at 'hidden epidemic.'")**

1. What is Eppin, which researchers are examining in male contraceptive research?

A. A testis/epididymis-specific protein
B. A prostate-sparing androgen
C. A phosphodiesterase
D. A GnRH antagonist

2. In the clinical trial of the contraceptive implant Implanon, what was the primary reason for discontinuation?

A. Nausea
B. Irregular bleeding
C. Amenorrhea
D. Breast tenderness

3. What is the drug recommended by the Centers for Disease Control and Prevention for treatment of lymphogranuloma venereum?

A. Penicillin
B. Tetracycline
C. Doxycycline
D. Azithromycin

4. Which of the following is NOT an advantage of extended regimens of contraception?

A. Convenience
B. Increased ovulation suppression
C. Minimized cyclic symptoms
D. Weight loss

Answers: 1. A; 2. B; 3. C; 4. D.

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.*