CONTRACEPTIVE TECHNOLOGY UPDATE®

Interpreting News and Research on Contraceptives and STIs

May 2011: Vol. 32, No. 5
Pages 49-60

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Financial Disclosure:
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Female condoms hit the spotlight — Will U.S. women see more options?

Candidates such as Woman's Condom, Origami may boost use

Since its introduction in 2009, use of the non-latex FC2 Female Condom (Women's Health Co., Chicago) has grown. In fact, the number of FC2s distributed in the United States tripled in the past year.[1]

The cost of a pack of three FC2 Female Condoms ranges between $5.99 and $7.99.[2]

The FC2 is enjoying success in Washington, DC, where all 55 CVS drug stores carry it, and public heath officials in San Francisco kicked off a new FC2 awareness campaign on Feb. 14, 2011. Houston public health officials followed suit in March 2011 by initiating their own awareness campaign about the barrier protection method.

However, as family planners know, options in choice might encourage more women in selecting a prevention method. Two new female condoms are on the horizon: the Woman's Condom developed by PATH in Seattle, and the Origami, under research by Strata Various Product Design in Culver City, CA.

EXECUTIVE SUMMARY

Since its introduction in 2009, use of the non-latex FC2 Female Condom has grown. On the horizon, two new female condom products could expand women's options for dual protection: the Woman's Condom, developed by PATH, and the Origami, under research by Strata Various Product Design.

- The Woman's Condom, made of polyurethane, has incorporated input from couples in four countries to address issues that have hampered acceptability of previous female condom designs. The product has performed well in studies in China, South Africa, the United States, and other countries. Additional studies of its performance and effectiveness are being gathered in two U.S. studies.
- The Origami condom is fabricated from silicone. It is in early research.

The Woman's Condom is a thin polyurethane pouch with several features that distinguish it from other designs. The pouch is packaged into a thin capsule (similar to an OB tampon) that helps with handling and insertion. When the capsule is inserted in the vagina, it quickly dissolves, allowing the vaginal pouch to unfold. Four small foam shapes attached to the vaginal side of the pouch lightly adhere to the vaginal wall and help keep the pouch stable during sex.[3]

The sheath is made of 0.03 mm polyurethane film and allows good sensation and comfort. The soft, low profile outer ring fits snugly against the pubic region[4] *(To read more about the Woman's Condom, see the* Contraceptive Technology Update *article, "Second-generation female condom OK'd by FDA -- What's next for the U.S.?" June 2009, p. 61.)*

Condom performance is evaluated through performance and failure mode studies. These studies of the Woman's Condom in the United States, South Africa, and China indicate the Woman's Condom performs well during use, with few clinical failures. Two additional studies ongoing in the United States will provide additional data that will be submitted to the Food and Drug Administration (FDA). CONRAD, an Arlington, VA, reproductive health research organization, is conducting a performance and failure mode study, also including prostate specific antigen (PSA) as a biomarker of semen exposure. Results from this study are expected by the end of 2011. The Eunice Kennedy Shriver National Institute of Child Health and Human Development is conducting a pivotal contraceptive effectiveness study of the Woman's Condom during 2011 and 2012. Data will be submitted to FDA as part of a premarket approval application, according to Patricia Coffey, MPH, PhD, Woman's Condom team leader and senior program officer at PATH.

Clinical studies in several countries indicate good acceptability with the Woman's Condom.[3, 5-6] PATH recently received a four-year grant from the Netherlands Ministry of Foreign Affairs that will support additional production scale up, regulatory applications, and production introduction in China and sub-Saharan Africa. This new product development partnership, known as Protection Options for Women Product Development Partnership, seeks to advance the Woman's Condom and expand affordable protection options for women. Other partners include the Shanghai (China) Dahua Medical Apparatus Company, CONRAD, and the Eunice Kennedy Shriver National Institute of Child Health and Development.

Progress is being made in bringing the Woman's Condom to diverse markets. In December 2010, the condom was granted CE Mark approval. The approval certifies the condom meets product quality standards for marketing in European

Contraceptive Technology Update® (ISSN 0274-726X), including STI Quarterly™, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Contraceptive Technology Update®, P.O. Box 105109, Atlanta, GA 30348.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291. E-mail: (customerservice@ahcmedia.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. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Back issues, when available, are $75 each.(GST registration number R128870672.)

Editor: **Rebecca Bowers.**
Executive Editor: **Joy Daughtery Dickinson** (229) 551-9195 (joy.dickinson@ahcmedia.com).
Production Editor: **Neill L. Kimball.**

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Editorial Questions

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

Union countries. In addition, Dahua has submitted an application to the China Food and Drug Administration for clearance to market the Woman's Condom in China. Response is anticipated in early 2011.

Origami in early studies

Further out in the research pipeline is the Origami female condom. The condom is made of a uniquely formulated silicone, says **Ray Chavez**, project coordinator at Strata Various Product Design in Culver City, CA. The material has been independently lab tested to have zero viral permeability using one of the smallest viruses known, the Phi-X174 bacteriophage, states Chavez. The silicone has high elongation and tensile strength properties to guard against breakage.

The Origami is designed with a no-fumble insertion method, part of a patent-pending feature based on a user-friendly telescoping design. The condom is inserted as a small dome-shaped cap that lodges in the vagina. The condom then deploys to its full length at the start of intercourse.

According to Chavez, the Origami is designed to optimize pleasure for both partners and simultaneously increase safety. The material is intended to simulate the properties of human tissue to resemble "sex-without-a-condom." "This is intended to make the [condom] more attractive to both men and women and increase correct and consistent female condom usage for those at risk," states Chavez.

Future studies will address the condom's potential as a reusable device for married couples. Preliminary experiments indicate the material can support multiple rigorous washings, cleaning agents such as bleach, and even microwave heating, says Chavez. The product also is designed to tolerate temperatures up to 425°F, which could help to extend its shelf life, he notes.

Research and development efforts to refine Origami prototypes were scheduled to be completed by April 2011. Preliminary prototypes were scheduled for human testing beginning in May 2011, with testing completed in February 2012. Phase I research, funded by the National Institutes of Health, is being conducted in collaboration with the Women's Global Health Imperative at the San Francisco office of RTI International, says Chavez.

The protocol includes two human volunteer studies. First is a user preference study, which will evaluate the design preferences and non-coital aspects of acceptability to identify which prototype is the most comfortable and acceptable. The second study is a couples' acceptability and performance study, which will compare the performance and acceptability of the preferred condom prototype during sex to that of commercially available condoms. A Phase II study will follow. If successful, commercialization plans are anticipated mid-year in 2014, says Chavez.

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Do more pill packs mean fewer pregnancies?

What is your facility's policy on providing multiple pill packs? Results of a new study might make you rethink your strategy. Researchers report that rates of unintended pregnancies and abortions decrease significantly when women receive a one-year supply of oral contraceptives, instead of being prescribed one- or three-month supplies.[1]

Researchers at the Bixby Center for Global Reproductive Health; the Department of Obstetrics, Gynecology, and Reproductive Sciences; and San Francisco General Hospital, all affiliated with the University of California, San Francisco (UCSF), linked 84,401 women who

received oral contraceptives in January 2006 through Family PACT (Planning, Access, Care, Treatment), a California family planning program, to Medi-Cal data showing pregnancies and births in 2006. Through Family PACT, some family planning clinics are able to dispense a one-year supply of pills on-site.

Analysis results showed a 30% reduction in the odds of pregnancy and a 46% decrease in the odds of an abortion in women given a one-year supply of birth control pills at a clinic versus women who received the standard prescriptions for one- or three-month supplies.

While oral contraceptives are highly effective when used correctly, statistics show about half of women regularly miss one or more pills per cycle, a practice associated with a much higher pregnancy rate: 80 pregnancies per 1,000 women in the first year of use.[2]

Other studies have shown that women will continue on their pill regimens with advance provision of pills, says **Anita Nelson**, MD, professor in the obstetrics and gynecology department at the David Geffen School of Medicine at the University of California in Los Angeles.[3]

What's the holdup?

What might impede programs from providing multiple pill packs to contracepting women?

According to an upcoming study that looked at national dispensing trends from 1996-2006, 44% of Pill users obtained one pack per purchase, with 27% receiving 2-3 packs per purchase, and 29% receiving more than four packs per purchase.[4]

EXECUTIVE SUMMARY

Researchers report that rates of unintended pregnancies and abortions decrease significantly when women receive a one-year supply of oral contraceptives, instead of being prescribed one- or three-month supplies.

- Researchers linked 84,401 women who received oral contraceptives in January 2006 through Family PACT (Planning, Access, Care, Treatment), a California family planning program, to Medi-Cal data showing pregnancies and births in 2006.
- Analysis results showed a 30% reduction in the odds of pregnancy and a 46% decrease in the odds of an abortion in women given a one-year supply of birth control pills at a clinic versus women who received the standard prescriptions for one- or three-month supplies.

These data indicate that resupply visits are the norm for most women on oral contraceptives, comments **Diana Greene Foster**, PhD, associate professor in the UCSF Department of Obstetrics, Gynecology, and Reproductive Sciences and director of research, advancing new standards in reproductive health at the university's Bixby Center for Global Reproductive Health. "How many packs women get depends on their source of care," states Foster, lead author of the multiple pill pack research paper. "And every program and insurance plan seems to have its own limit."

Most state Medicaid programs routinely limit the amount of prescription drugs dispensed in pharmacies to a 30- to 34-day supply, notes Foster. Some federally supported family planning waiver programs for low-income women without Medicaid permit clinics to dispense a one-year supply, observes Foster. "For example, waiver programs in California, Oregon, Alabama, Virginia allow this [form of dispensing]," says Foster. "This benefit isn't available in every state, and it doesn't work for women who do qualify for Medicaid or get their prescriptions filled at pharmacies rather than clinics."

What will it take to change dispensing practice? State Medicaid programs, family planning waiver programs, and private health insurance plans could change their policy and allow a one-year supply in recognition of the potential cost savings, reduction in unintended pregnancy, and improvement in quality of care, says Foster.

Earlier analysis by Foster's research team showed that dispensing a year's supply of pills saves money simply by avoiding unnecessary repeat resupply visits.[5] *(To read more about the research, see the* Contraceptive Technology Update *article, "Break down barriers to contraceptive access; provide multiple pill packs," February 2007, p. 13.)* The team's new research indicates that savings are likely much greater when the expense of unwanted pregnancies is included. Both in terms of quality of care and cost avoidance, it makes sense to offer one-year contraceptive supplies as a program benefit, says Foster.

If the 65,000 women in the analysis who received one or three packs of pills at a time had experienced the same pregnancy and abortion rates as women who received a one-year supply, almost 1,300 publicly funded pregnancies and 300 abortions would have been averted, according to Foster's research team. "The evidence indicates that health plans and public health programs may avoid paying for costly unintended pregnancies

by increasing dispensing limits on oral contraceptives," says Foster. "Improving access to contraceptive methods reduces the need for abortion and helps women to plan their pregnancies."

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New patch options — Could they catch on?

When the Ortho Evra transdermal contraceptive (Ortho Women's Health & Urology, Raritan, NJ) was introduced in 2002, use of the patch caught on quickly with young women. However, pharmacokinetic data indicated the release of ethinyl estradiol (EE) from the first-generation patch was associated with substantially higher area under the curve for EE than low-dose contraceptives.[1-4]

Research is investigating two new contraceptive patch options. One patch under development delivers a low dose of estrogen in combination with levonorgestrel, and is applied once weekly for three weeks, followed by a patch-free week. The second option is a low-dose, progestin-only contraceptive patch designed to provide an option for women for who estrogen-containing contraceptives are contraindicated, inappropriate, or unwanted. Agile Therapeutics of Princeton, NJ, is developing both patches.

The high estrogen impact of the first generation Evra patch, the related warning added to the patch package label, and highly publicized reports of cardiovascular events with patch users all resulted in a "boom bust" phenomenon, observes **Andrew Kaunitz**, MD, professor and associate chair in the Department of Obstetrics And Gynecology at the University of Florida College of Medicine – Jacksonville. After initial rapid uptake of the patch, use of the contraceptive option rapidly lost popularity among U.S. women. "From this perspective, a lower estrogen transdermal contraceptive would be a most welcome addition to the cafeteria of contraceptive choices we offer our patients," says Kaunitz. *(To review the history of the Evra patch, see the* Contraceptive Technology Update *articles, "FDA updates study data information on Ortho Evra contraceptive patch labeling," April 2008, p. 37, and "FDA revises Evra safety labeling due to increased estrogen levels," January 2006, p. 1.)*

Research now emerges

Agile Therapeutics' AG200-15 is a weekly combination hormonal contraceptive patch containing the active ingredients levonorgestrel (LNG) and ethinyl estradiol (EE), both of which have a well-established history of efficacy and safety in combination contraceptives, says **Marie Foegh**, MD, the company's chief medical officer and vice president of clinical research and development. The patch is applied once weekly for three weeks, followed by a fourth patch-free week.

Results of a pivotal pharmacokinetic study presented at the 2010 annual meeting of the American Society of Reproductive Medicine indicate the low daily dose of EE delivered by the AG200-15 patch was comparable to a low-dose oral contraceptive

EXECUTIVE SUMMARY

Research is investigating two new contraceptive patch options. Both patches are being developed by Agile Therapeutics of Princeton, NJ.

- One patch under development, AG200-15, delivers a low dose of estrogen in combination with levonorgestrel. It is applied once weekly for three weeks, followed by a patch-free week. Enrollment has been completed in two pivotal Phase 3 trials.
- The second option is a low-dose, progestin-only contraceptive patch designed to provide an option for women for whom estrogen-containing contraceptives are contraindicated, inappropriate, or unwanted. A pharmacokinetic and pharmacodynamic study has been initiated, and enrollment is ongoing.

at 30 mcg per day.[5]

Agile has completed enrollment in the two pivotal Phase 3 trials for AG200-15, according to Foegh. Recruiting and enrollment of patients began in August 2010, with more than 1,500 women enrolled in just eight weeks, she notes. "This rapid enrollment exceeded expectations and has been attributed to the interest among patients in the option of a patch for contraception," says Foegh. "The study will be completed in the fourth quarter of 2011. It is our goal to submit the NDA [new drug application] in the first quarter of 2012."

What is the research status of the low-dose, progestin-only contraceptive patch? Known as AG900, the patch delivers a controlled dose of levonorgestrel. The regimen is continuous, with women replacing the patch every seven days with no "patch-free" period, says Foegh. The delivery of the drug eliminates some of the challenges associated with progestin-only options, says Foegh.

Clinical trials are being conducted through a clinical trial agreement with the National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. A key pharmacokinetic and pharmacodynamic study has been initiated, and enrollment is ongoing, she states.

Look for more information on patch development. AG200-15 data will be presented in two posters at the upcoming American College of Obstetrics and Gynecology 2011 Annual Meeting in Washington, DC, April 30-May 4. *(Look for further coverage in an upcoming issue of* Contraceptive Technology Update.*)*

Data from AG200-15 clinical trials has been presented at various medical meetings, says Foegh. Full publications of these studies are in process, with the first manuscript now in press in the Journal of Hormone Molecular Biology and Clinical Investigation, she states.

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Low-literacy material targets correct OC use

You have just reviewed instructions on proper oral contraceptive (OC) use with your patient, a 22-year-old mother of three. You ask if there any questions and send her to the front desk with a supply of pill packs and written instructions. But how do you know she received the information she needs to take her pills properly?

Providing low literacy materials with easy-to-follow instructions is essential in reducing the U.S. unintended pregnancy rate and its associated annual costs of $2.6 billion.[1] However, clinicians face an uphill battle. The National Center for Education Statistics estimates that 88% of the adult U.S. population lacks the literacy skills needed to maintain health and prevent disease.[2]

In response to a request by Title X family planners, a cooperative effort among the Region VI Department of Health and Human Services Office of Family Planning, the Center for Health Training in Austin, and Sage Words Accessible Health Communications in Austin has yielded an oral contraceptive health literacy project to help providers and patients communicate more effectively regarding correct, consistent pill-taking. The project, "On the Same Page," features a training manual written for publicly funded family planning clinic staff, as well as posters designed to help clinicians and patients stay "on the same page" during instructions. Patient materials include a missed pills business card and flyers on missed pills, starting pills, and side effects, all available in English and Spanish. The project was funded by a

grant from the Department of Health and Human Services, Office of Population Affairs, Office of Family Planning, Region VI. *(For information on how to access the manual and project materials, see resources, bottom left.)*

How does it work?

Clinicians are accustomed to thinking of written materials as something to hand to patients. The posters and fact sheets in the "On the Same Page" project work together as a tool, something that is used interactively, much in the same way clinicians use the pill packet for demonstration, say project officials.

The poster concept came directly from staff discussion groups, explains **Kathryn Anderson**, MA, executive director of Sage Words Accessible Health Communications. Anderson served as writer and developer for the project. "When we asked what format would be useful to them, staff indicated that posters were a useful and familiar format. Staff often used posters in an exam room setting, especially to communicate visually," she explains. "We also learned from staff discussion groups that they rarely use written materials like brochures or the pill packet insert in the exam room when explaining pill instructions."

Materials with small fonts, a significant amount of text, and no graphics simply can't be shared, says Anderson. A poster, on the other hand, is visually accessible to provider and patient. Graphics and text can be seen at the same time, so the patient is a participant in the provider's explanation.

A second important aspect of using the posters in the exam room is that the patient has access to the same information more than once, Anderson notes. Repetition is essential in processing unfamiliar information and in retaining and acting on that information, she explains. If the patient has been sitting in the exam room looking at the poster, it might serve to elicit questions. Anderson says it also might serve as an "advance organizer" in which the patient might already have begun the process of organizing and understanding the information before the provider discusses it with her. The patient can see the poster ahead of the provider's visit, looks at it while the provider discusses the information, and has the same information at home on the fact sheet, Anderson states. Having exactly the same information in the same format at home might help a patient trigger recall of the exam room discussion, which can be helpful in comprehending the written information, explains Anderson. Patients tested drafts of the text in a process called usability testing, which enabled developers to pinpoint and revise areas of misunderstanding. *(Use the information on p. 56 to help integrate telephone and cell phones into reinforcing the written message.)*

Title X grantees in Region VI, which encompasses Arkansas, Louisiana, Oklahoma, New Mexico, and Texas, have been excited about the materials included with the project, says **Sandy Rice**, MEd, vice president of the Center for Health Training. Project funding allowed developers to be able to provide a year's worth of hard copies of the "missed pills" fact sheets and posters to grantee clinics in the region. "Although we are pleased and proud that we have made these materials available online for free download, we recognize that Title X and other publicly funded clinics face severe budget restrictions that may prohibit their abilities to make copies," says Rice.

EXECUTIVE SUMMARY

A cooperative effort among the Region VI Department of Health and Human Services Office of Family Planning, the Center for Health Training in Austin, and Sage Words Accessible Health Communications in Austin has yielded an oral contraceptive health literacy project to help providers and patients communicate more effectively regarding correct, consistent pill-taking.

- The "On the Same Page" project features a training manual written for publicly funded family planning clinic staff, as well as posters designed to help clinicians and patients stay "on the same page" during instructions.
- Patient materials include a missed pills business card and flyers on missed pills, starting pills, and side effects, all available in English and Spanish.

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RESOURCES

The manual and project materials for "On the Same Page," an oral contraceptive health literacy project, are available

for free download at the Center for Health Training web site, www.centerforhealthtraining.org. Under "Projects," select "Current Projects," then under "Region VI," select "Health Literacy Project: Oral Contraceptive Patient Education Materials." Clinicians also can take advantage of a free webinar on the project. To access the webinar, go to www.centerforhealthtraining.org. Under "Training + Events," select "Online Training." To access the webinar, click the link under "Health Literacy and OCPs: Helping Your Clients to Understand and Remember Instructions for How to Use OCPs Correctly."

• Oral contraceptive health literacy materials also are available at www.sagewords.org. ■

Reinforce message with phones, cells

How can you bolster your patients' understanding of correct oral contraceptive use after they leave the office? Try these tips from the On the Same Page *OCP Health Literacy Project Training Manual*:

• Have someone at your clinic read the text from the material into a recorded phone message.

• Have the recorded phone message on an extension of your clinic phone that can be reached day or night.

• Help your patient program the clinic telephone number/extension into her cell phone while she is in the exam room.[1]

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Antidepressant eyed to reduce hot flashes

[Editor's note: This story discusses off-label use of the antidepressant medication escitalopram (Lexapro, Forest Laboratories, New York City).]

For women with hot flashes associated with menopause, clinicians have long looked to hormonal agents as the predominant treatment option. Use of hormone therapy has greatly decreased since the Women's Health Initiative (WHI) estrogen plus progestin randomized trial combination hormon therapy highlighted risks associated with combination hormone therapy. No other treatments for menopausal hot flashes have Food and Drug Administration (FDA) approval.[1,2] *(To obtain more information on WHI research, see the* Contraceptive Technology Update *articles "Hormone therapy: Make decisions on a balanced risk-to-benefit basis," April 2003, p. 37, and "Hormone replacement therapy: Review choices in light of new data," September 2002, p. 97.)*

Scientists are looking at safe, effective options for menopausal therapy. News is just in from a scientific initiative of alternative treatments funded by the National Institutes of Health's National Institute of Aging, with the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Center for Complementary and Alternative Medicine, and the Office of Research on Women's Health. In a study that looked at use of the antidepressant medication escitalopram (Lexapro, Forest Laboratories, New York City), results suggest women who were in the transition to menopause or postmenopausal experienced reduced frequency and severity of menopausal hot flashes with the drug, compared to women who received placebo.[3] Use of the drug for hot flash treatment is considered off-label by the FDA.

"Our findings suggest that among healthy women who were not depressed or anxious, a 10 to 20 mg dose of escitalopram, which is well below the dosage level for psychiatric use, provides a nonhormonal, off-label option that is effective and well-tolerated in the management of menopausal

EXECUTIVE SUMMARY

In a scientific initiative of alternative menopausal treatments, a study looked at the antidepressant medication escitalopram (Lexapro, Forest Laboratories, New York City). Results suggest women who were in the transition to menopause or postmenopausal experienced a reduction in the frequency and severity of hot flashes with the use of the drug, compared to women who received placebo. Symptom relief with escitalopram is substantially less than that shown in studies using hormone therapy.

• Use of the drug for hot flash treatment is considered off-label by the Food and Drug Administration.

• A second study is researching the effectiveness of yoga, exercise, or omega-3 supplementation for relieving menopausal symptoms.

hot flashes," says **Ellen Freeman**, PhD, principal investigator of the national, multi-site study and research professor of obstetrics and gynecology at the University of Pennsylvania School of Medicine in Philadelphia.

Investigators enrolled 205 women between July 2009 and June 2010 to conduct the eight-week trial. Women were randomized to receive 10 mg per day of escitalopram or a matching placebo pill for eight weeks.

If women did not report a reduction in hot flash frequency of at least 50% or a decrease in hot flash severity after four treatment weeks, the study medication dose was increased to 20 mg per day (or matched placebo) without unblinding the randomization. Primary outcomes included frequency and severity of hot flashes assessed by prospective daily diaries at weeks four and eight.

Researchers report the average frequency of hot flashes at the beginning of the study at 9.8 per day. Use of the study drug was associated with a reduction in the frequency of hot flashes relative to placebo, adjusted for race, site, and baseline hot flash frequency. In the escitalopram group, average hot flash frequency at week eight decreased to 5.26 hot flashes per day, a 47% decrease. A three-week study participant follow-up also showed that hot flashes increased after cessation of escitalopram but not after cessation of placebo, further indicating the effectiveness of the drug.[3] Symptom relief with the escitalopram treatment is substantially less than that which is achieved with hormone therapy; results of hormone therapy trials show 80-90% symptom relief.[4,5]

Options now in review

The report is the first published research from the National Institutes of Health's Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH), a network of research studies looking at treatments for common symptoms of menopause.

The network is conducting several randomized clinical trials to test a variety of approaches for treating menopausal symptoms, including use of anti-depressant medications, yoga, omega-3 supplementation, exercise, and low dose estrogen gel. Participants in the studies are women ages 40-62 who live in Boston, Indianapolis, Oakland, Philadelphia, and Seattle.

Scientists are enrolling women into a second study. The second study will examine the effectiveness of yoga, exercise, or omega-3 supplementation for relieving menopausal symptoms. Centers at the Indiana University School of Medicine in Indianapolis, Kaiser Permanente, Northern California in Oakland and the Group Health Center for Health Studies and the University of Washington School of Medicine, both in Seattle, are participating. The intervention period is 12 weeks, says **Sherry Sherman**, PhD, program director of Clinical Aging and Reproductive Hormone Research at the National Institute on Aging. "For decades, estrogen with or without progesterone has been the treatment of choice for relieving menopause-related symptoms because of the lack of alternative therapies of comparable proven efficacy," said Sherman. "The collaborative, multidisciplinary, multicenter approach of MsFLASH will enable researchers to test other options, including behavioral and complementary and alternative medicine approaches, to determine whether they are also effective against hot flashes."

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Research eyes chlamydia, ectopic pregnancy link

A ruptured ectopic pregnancy is the leading cause of maternal mortality in the first trimester and accounts for 10 to 15% of all maternal deaths.[1-3]

A history of diagnosed chlamydial infection is associated with a two-fold increased risk for ectopic pregnancy.[4] However, the extent to which

such infection accounts for the adhesions, tubal alteration, and damage that predispose women to the condition remains largely unknown. The link between chlamydia and ectopic pregnancy is of concern for family planning clinicians, as chlamydia is the most frequently reported bacterial sexually transmitted disease in the United States. In 2008, more than 1.2 million chlamydial infections were reported to the Centers for Disease Control and Prevention from 50 states and the District of Columbia.[5]

Results from a new study indicate how chlamydia can increase the risk of an ectopic pregnancy.[6] Researchers at the University of Edinburgh in Scotland have found that women who had had the sexually transmitted infection were more likely to produce a particular protein in their Fallopian tubes. Increased production of the protein, known as PROKR2, makes a pregnancy more likely to implant in the Fallopian tube, the scientists state.[6] The current study follows previous research by the University of Edinburgh team, which showed that production of a similar protein increased the likelihood of smokers having an ectopic pregnancy.[7]

"We know that chlamydia is a major risk factor for ectopic pregnancy, but until now we were unsure how the infection led to implantation of a pregnancy in the Fallopian tube," said **Andrew Horne**, PhD, MRCOG, clinician scientist and honorary consultant in obstetrics and gynecology at the University of Edinburgh, in a statement accompanying the publication. "We hope that this new information allows health care providers to give women accurate information about risks following chlamydial infection and to support public health messages about the importance of safer sex and chlamydia testing."

Blood test in wings?

Could a blood test indicate the presence of an ectopic pregnancy? Current diagnosis relies on the use of ultrasound.

Researchers at the Wistar Institute and the University of Pennsylvania School of Medicine, both in Philadelphia, identified protein markers that might serve as the first reliable blood test to predict ectopic pregnancies. Their research is available online in the *Journal of Proteome Research*.[8]

A related small-scale study of clinical samples indicates that one of the proteins identified in the online publication, ADAM12, showed a nearly 97% correlation with ectopic pregnancy.[9]

In the online publication, scientists compared the proteomic signature of blood samples taken from known cases of ectopic pregnancy with blood samples taken from women who experienced a normal pregnancy. About 70 candidate biomarkers were identified that could signal ectopic pregnancy. Statistical analysis narrowed the field to the 12 most promising biomarkers. While some of the proteins previously had known associations with ectopic pregnancies, the researchers found at least two, including ADAM12, which previously had never been associated with ectopic pregnancy.

The scientists now plan to further confirm and validate the usefulness of the identified panel of biomarkers. By using additional patient samples, they hope to create a practical, reliable blood test for ectopic pregnancy. Among their goals is to identify particular isoforms (variations of a given protein) that are most relevant to identifying ectopic pregnancy. "The great power of biomarkers is to detect clinical disorders such as ectopic pregnancy or diseases, such as cancer, early when it is often easiest to treat the patient," said **David Speicher**,

EXECUTIVE SUMMARY

Results from a new study indicate how chlamydia can increase the risk of an ectopic pregnancy. Researchers at the University of Edinburgh in Scotland have found that women who had had the sexually transmitted infection were more likely to produce a particular protein in their Fallopian tubes.

• Increased production of the protein, known as PROKR2, makes a pregnancy more likely to implant in the Fallopian tube, the scientists state.

• U.S. researchers have identified protein markers that might serve as the first reliable blood test to predict ectopic pregnancies. A ruptured ectopic pregnancy is the leading cause of maternal mortality in the first trimester and accounts for 10-15% of all maternal deaths.

COMING IN FUTURE MONTHS

■ Science explores potential spermicide

■ Syphilis screening under review

■ Public health focuses on spread of HIV/AIDS in women

■ What is the best way to present risk statistics to your patients?

PhD, professor and co-leader of Wistar's Molecular and Cellular Oncogenesis Program and director of Wistar's Center for Systems and Computational Biology. "Here we can envision a useful blood test that could, as part of routine early prenatal care, save the lives of many women."

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CNE/CME INSTRUCTIONS

Physicians and nurses participate in this continuing nursing 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 issue, you must complete the evaluation form provided and return it in the reply envelope provided in that issue to receive a letter of credit. When your evaluation is received, a letter will be mailed to you. ■

CNE 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;
- describe how those issues affect services and patient care;
- integrate practical solutions to problems and information into daily practices, according to advice from nationally recognized family planning experts;
- provide practical information that is evidence-based to help clinicians deliver contraceptives sensitively and effectively.

17. What material is used to make the Woman's Condom?
A. Polyurethane
B. Silicone
C. Latex
D. Nitrile

18. According to the results of a new study in *Obstetrics & Gynecology* (2011;117:566-572), rates of unintended pregnancies and abortions decrease significantly when women receive which amount of oral contraceptives?
A. One-month supply
B. Three-month supply
C. Six-month supply
D. One-year supply

19. What are the hormones contained in Agile Therapeutics' AG200-15, a weekly combination hormonal contraceptive patch under development?
A. Levonorgestrel and ethinyl estradiol
B. Norgestimate and ethinyl estradiol
C. Norethindrone acetate and ethinyl estradiol
D. Levonorgestrel only

20. What antidepressant medication is the focus of a current study in *The Journal of the American Medical Association* (2011; 305:267-274) that examines alternative treatment for menopausal hot flashes?
A. Citalopram
B. Escitalopram
C. Fluoxetine
D. Sertraline

Answers: 17. A; 18. D; 19. A; 20. B

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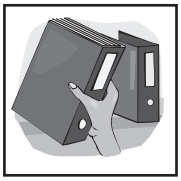

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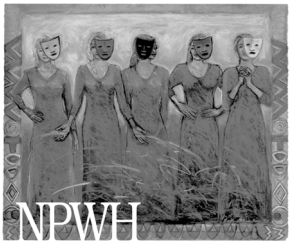

Association of Reproductive Health Professionals

OB/GYN
QUARTERLY UPDATE

Intrauterine devices are on the move — Your most pressing questions addressed

By **Regina-Maria Renner**, MD, MPH, Fellow in Family Planning and
By **Alison Edelman**, MD, MPH, Associate Professor, Assistant Director of the Family Planning Fellowship, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland

Case presentation

A 25-year-old G3P1021 presents to clinic concerned that her intrauterine device (IUD) strings feel longer. She is otherwise asymptomatic. Her IUD was placed five months earlier without complications, and it was noted that her stings were cut to 3 cm. On exam, the IUD strings are 4 cm long. The exam is otherwise unremarkable, and the IUD stem cannot be seen or felt. An ultrasound shows a copper IUD in the lower uterine segment, but above the cervix. What now? This case scenario might generate several questions and/or concerns. Is your inclination to remove the IUD? If so, wait and read further.

Where in the uterus does the IUD normally "live"?

Faundes et al prospectively followed a cohort of 214 women after copper T IUD (CuIUD, Paragard) insertion.[1] With serial ultrasound exams, they assessed several measurements that were performed at insertion, 30 days later, and 90 days later. Most women had an IUD-to-myometrium distance that increased with time (distance at insertion: 7 mm; 30 days: 9 mm; 90 days: 10 mm). Based on this information, they defined "correct" placement with an IUD-to-myometrium cutoff measurement of 7 mm. In applying this measurement at the time of insertion and at 90 days, 17 and 21 IUDs were considered "misplaced." Leaving these IUDs in situ revealed that only six remained "misplaced" after 90 days, one expelled (but this IUD actually had been in a normal position at 30 days), and two were found to be in the intracervical canal and removed. No pregnancies were reported during the study.

This study illustrates that IUD position is not static and there is a small amount of movement within the uterine cavity, especially in the vertical direction between the fundus and lower uterine segment. More importantly, visualizing the IUD in the lower uterine segment or using a cutoff measurement to define "misplacement" did not predict expulsion. Additionally, some of these measurements can vary significantly during the menstrual cycle, 5 mm or more, secondary to endometrial thickness.

A retrospective cohort study of 214 women assessed IUD location using ultrasound over six months after insertion of a Multiload375 (ML375) IUD (a copper-based IUD) (n = 107) or a levonorgestrel-releasing (LNG) IUD (n = 107).[2] The distance between the top of the IUD and the junction between endometrium and uterine cavity (IUD-ED) was measured. Investigators defined a "partial expulsion" as an IUD-ED > 10 mm, and they recommended removal based on this definition. Partial and complete expulsions were not

Statement of Financial Disclosure:

Regina-Maria Renner, MD, MPH, guest author, reports no financial relationship to this field of study. **Alison Edelman**, MD, MPH, guest author, is a subdermal implant trainer for Merck. **Frank W. Ling**, MD, guest author, reports no financial relationship to this field of study. Peer reviewer **Catherine LeClair**, MD, and Executive Editor **Joy Dickinson** report no financial relationship to this field of study.

reported separately in this study. The IUD groups did not significantly differ regarding age, parity, sounded uterine length, or history of IUD expulsion. Correct position was verified at the time of insertion.

At six weeks, partial or complete expulsion was noted in 11% in the ML group vs 4% in the LNG group (P = 0.06). At six months, partial or complete expulsion again was noted to be higher in the ML group (P < 0.05). Partial or complete expulsion was found to be associated with increasing parity and history of IUD expulsion. Again, no pregnancies were observed. This study concluded that LNG IUDs have a lower expulsion rate; however, the data are insufficient to draw such conclusions. ML375 IUDs are known to have higher expulsion rates than T-shaped devices, such as the LNG- and Cu-IUDs.[3]

When and how should we assess IUD location?

In a prospective cohort of 436 CuIUD users, Petta et al studied transvaginal ultrasound to assess correct IUD location.[4] Groups received an ultrasound at 30-40 days post-insertion vs clinical exam alone. This study defined "correct" placement as less than 3 mm between IUD and endometrium at the fundus. Women were matched by age and parity and followed for one year to determine expulsion rates. This study did not separate true expulsions from those removals performed for an IUD position of more than 3 mm from the endometrium.

Among the ultrasound cohort (n = 235), 34 IUDs were found to be "misplaced" and were removed; 22 had a new IUD inserted, of which seven expelled later. One true expulsion was found in the ultrasound cohort. In the routine care group, 10 women experienced true expulsions. One pregnancy occurred in the latter group at 11 months. Although the ultrasound cohort had a lower number of "true" expulsions, the total number of IUDs removed due to an arbitrary cutoff value makes the number needed to treat to support the routine use of ultrasound unreasonably high, or 34 IUD removals to prevent nine expulsions. It's likely that most of these removals were unnecessary and would not have ended in expulsion since Faundes showed the IUD to endometrium measurement varies significantly during the cycle.[1] In addition, not all of these 34 women chose to have another IUD, which means they are probably using a less effective method of birth control. Finally, the number of expulsions that occurred in the routine care group is higher than expected (4%), which makes one think there were insertion technique issues in this group as compared to the ultrasound group. As groups were enrolled based on days of the week, perhaps less experienced providers were placing IUDs in this group?

De Kroon et al also assessed the use of ultrasound to monitor the position of an IUD after insertion.[5] This prospective cohort of 195 women with high study retention (93%) compared serial clinical IUD string length with ultrasound at the time of insertion and six weeks thereafter. A distance of more than 5 mm between IUD and endometrium on ultrasound was considered "dislocated." Although various IUD types were included in the study, more than half were LNG IUDs (58.5%). Immediately after insertion, ultrasound identified 7.7% of IUDs as "dislocated"; six weeks thereafter, only 4% were identified as dislocated. Consistent with the results of the Faundes et al[1] study, the majority of IUDs classified as "dislocated" were normally positioned at six weeks.

The clinical string check had a high negative predictive value immediately after insertion (NPV 0.98 [95% confidence interval 0.96-1.0]) as well as six weeks later (NPV 1.0 [0.98-1.0]). In other words, if the strings appeared to be the appropriate length, the IUD was in the uterine cavity. The positive predictive value for clinical string check was lower (PPV 0.6 [0.39-0.81] and 0.54 [0.26-0.81], respectively). If the strings appeared longer, that did not always mean the IUD was incorrectly positioned. This supports a strategy of performing a clinical string check first. If normal, no further workup is needed, but if there is concern, an ultrasound might be useful. Interestingly, all the women in this study with an abnormal IUD position at six weeks were symptomatic, which also supports reliance on good history and physical exam skills. No pregnancies were observed.

Is a low-lying IUD still effective?

The IUD is one of the most effective birth control methods available to women. First-year typical-use failure rate is 0.8% for the CuIUD and 0.2% for the LNG IUD, and continuation rates are high at 78–80%. These very low failure rates make it challenging to perform a study with enough power to examine if low-lying IUDs fail more often. This explains the paucity of data and the mostly retrospective and observational data on this particular topic.

Unfortunately, the published studies currently available do not allow us to differentiate what came first: the pregnancy or the IUD dislocation. IUD failure and its relationship to intrauterine location was investigated by Anteby et al.[6] A prospective cohort of 100 women had a ML375 IUD placed. Of these, 97 underwent ultrasound 45-60 days post-insertion. They found that 7.2% had an intracervical IUD location. Age and parity did not influence the IUD

location. They compared this information to a group of 25 pregnant women with an IUD in place. Of these women, 52% had an intracervical IUD and the rest were intrauterine.

A case control study by Inal et al examined IUD location in 318 pregnant women with an IUD and in 300 controls of non-pregnant women with an IUD.[7] Although 64% of IUDs were dislocated in the cases (defined as far from the fundus or arms rotated), only 11% were dislocated in the controls ($P < 0.05$). Realistically, the only conclusions that can be drawn from these studies are that an IUD is not located in the right place after a failure occurs, but it is unclear if it was in the right place before the failure occurred.

Using a theoretical approach, the copper IUD prevents pregnancy primarily by being spermicidal, while the LNG IUD thickens the cervical mucus, thins the endometrium, has some spermicidal function, and suppresses ovulation in some women. In both IUD types, the mechanism of action is more global in nature, which suggests that the exact location within the uterus should not matter.

Other outcomes of interest are spontaneous uterine expulsion and symptomatic IUD dislocation, since both require re-establishing effective contraception. If expulsion goes unnoted, it might lead to an undesired pregnancy. Spontaneous expulsion of the IUD occurs in 2-10% of users; nulliparity[8] and heavy menstrual flow are risk factors. As pointed out above, most women will complain of symptoms such as lengthening of the IUD string, pain, bleeding, or dyspareunia in the case of a partial expulsion (intracervical), and ultrasound has not been shown to effectively predict which IUD will expel.

We recommend leaving the IUD of above-presented patient and counseling her that it is effective. We would further counsel her to return to clinic in case of symptoms, such as pain, abnormal vaginal bleeding, or in if she cannot feel her strings.

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Heavy menstrual bleeds given new treatment

Abstract & Commentary

By **Frank W. Ling,** MD, Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, TN. Ling is associate editor for *OB/GYN Clinical Alert*.

Synopsis: In a double-blind, randomized, placebo-controlled trial, oral tranexamic acid was well tolerated and improved quality of life and menstrual blood flow in patients with heavy menstrual bleeding.

Source: Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: A randomized controlled trial. *Obstet Gynecol* 2010;116:865-875.

After two pretreatment cycles, 196 patients with menorrhagia were randomized to tranexamic acid or placebo. Ultimately, after accounting for patients lost to follow-up, adverse events, and protocol violations, there were 117 evaluable patients in the tranexamic acid group and 72 in the placebo group who received up to five days of either study drug or placebo for each of six cycles. The primary endpoint was reduction in menstrual blood flow. This was defined as overall blood loss compared to predetermined significant amount (36 mL) and meaningful reduction perceived by the patient. Quality of life factors also were measured in terms of limitations of activities and work in and outside of home. The tranexamic acid successfully exceeded the benefits of placebo in terms of clinical and quality-of-life measurements, while having a comparable side effects profile.

Commentary

How can you argue with a multicenter, ran-

domized, placebo-controlled trial? Don't be cynical just because it was sponsored by a drug company. The findings can be useful for your patients. I know it already has helped some of my patients.

Tranexamic acid is a competitive plasminogen inhibitor that has been used overseas for reduction of menstrual blood loss. Gastrointestinal side effects have been minimized with a new formulation, sold as Lysteda. Showing efficacy when compared to placebo would seem to be a "given" since this is a Phase 3 trial. Having already passed the scrutiny of the Food and Drug Administration, the drug must do what it claims to do. It's important, however, to note that this study prohibited the concomitant use of oral contraceptives and nonsteroidal anti-inflammatory drugs. In real life, many patients potentially could use one or both of these agents, so further studies could address how the drug performs in those settings.

So the drug is out there on your sample shelf already. You've likely been "detailed" on it by your friendly, neighborhood pharmaceutical representative. Why do I include this study? Because early in this same issue, there is a study comparing two second-generation endometrial ablation techniques (bipolar radiofrequency endometrial ablation and hydrothermablation, with the former being shown to be superior to the latter).[1] Here we have medical and surgical interventions being studied and reported on in the same issue of our most prestigious of journals.

I am hopeful that the significance of the juxtaposition of the two articles is not lost of any of us. Hopefully, nobody who has access to offering surgical/procedural interventions for menorrhagia is performing them without appropriate consideration of both old and new nonsurgical treatment options. Indeed, every patient might have preconceived notions of medical and surgical options and the appropriateness thereof. It is our job as women's health care advocates to make sure that each patient is given every opportunity to make a truly informed decision at each step. After all, as Yogi Berra said, "When you reach a fork in the road, take it." That advice reflects what each patient decision is: a choice. It needs to be supported by the best information that we can provide.

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Ovarian cancer screening: Will it impact mortality?

Abstract

Synopsis: Despite the survival differences between early and advanced stage ovarian cancer and the promise of "stage migration" with general population screening, modeling suggests the impact will be modest due to identification of low-risk disease.

Source: Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity. *Cancer* 2011;117:545-553.

Recent investigation into the molecular pathogenesis of epithelial ovarian cancer has implicated two dominant phenotypes. One manifests by late presentation, advanced stage, and an aggressive clinical course (Type I), and one manifests with a more indolent nature, which, despite an innate chemoresistance, is associated with long survival (Type II).

By studying the history of ovarian cancer, the authors evaluated the impact of screening on mortality. They considered a 1-phenotype and a 2-phenotype model, the latter including the assumptions on outcome based on the contribution of Type II cancers. To calibrate their data, they used data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. They also assumed their "screening model" would perform in line with the multimodal screening algorithm (MMS) in the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study, and they adjusted the SEER prevalence ovarian cancer rate to match the UKCTOCS study.

The authors showed their validation test of screening performance would increase stage I/II cancers to about 41%, in line with the UKCTOCS study. Positive predictive value also was close (26%-27% vs. 35%). Overall survival for ovarian cancer predicted based on the 1-phenotype and 2-phenotype model was similar to that expected from the SEER data. The impact on mortality from an implemented postmenopausal annual screening program resulted in an 11% (2-phenotype model) to 15% (1-phenotype model) reduction in mortality. Modeling different screening characteristics (sensitivity and specificity) and frequencies adjusted these measures only slightly, with the exception of the screening frequencies, which had its greatest impact with every-three-months evaluation. ■