CONTRACEPTIVE TECHNOLOGY UPDATE®
A Monthly Newsletter for Health Professionals



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# Time for Today sponge in Canada — will U.S. see vaginal contraceptive?

*Company is seeking FDA approval for marketing in United States*

Four years after its initial announcement to revive the Today contraceptive sponge, the company responsible for its rebirth finally has released the product in Canada and says it is pressing for Food and Drug (FDA) approval to market the device over the counter in the United States.

The sponge is available for sale over the Internet on two Canadian web sites, www.birthcontrol.com and www.feelbest.com, says **Robert Staab**, PhD, chairman and chief scientific officer of Allendale (NJ) Pharmaceuticals. At *Contraceptive Technology Update* press time, he predicted it would be on Canadian pharmacy shelves and other mass-merchandising outlets this month. The sponges are priced at the U.S. equivalent of about $2.90 each on the two web sites. While the sponge is not for sale in the United States, American women are ordering the device from the Canadian web sites.[1]

Women have awaited news of the sponge's re-emergence; some 250 million sponges were sold between Today's 1983 market debut and 1995 removal.[2]

### EXECUTIVE SUMMARY

The company responsible for the revival of the Today contraceptive sponge has released the device in Canada and continues to seek approval from the Food and Drug Administration (FDA) to market it in the United States.

- The FDA did not remove the sponge from the market; its former maker ceased production when it determined it cost too much to correct manufacturing problems.
- While the sponge represents convenient, user-controlled contraception, it is not the most effective method. In a recent review, the sponge was significantly less effective in preventing overall pregnancy than the diaphragm.

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The FDA did not remove the sponge from the market; its former manufacturer, Whitehall-Robins Healthcare of New York City, ceased production when it determined it cost too much to correct problems caused by water quality issues at the old factory where the sponge was made. Allendale Pharmaceuticals acquired manufacturing and marketing rights to the sponge in 1999. **(See the May 1999 *Contraceptive Technology Update* article, "Revival of the Today sponge: Vaginal contraceptive returns," p. 49, for a review of the sponge's manufacturing history.)**

Allendale Pharmaceuticals originally planned to reintroduce the sponge in the American market in fall of 1999. Tougher new FDA standards for manufacturing and record keeping resulted in repeated delays and a switch from a contract manufacturer in Mainland, PA, to OSG Norwich (NY) Pharmaceuticals.[1]

The contraceptive sponge still is under review, confirms **Susan Cruzan**, FDA spokeswoman. What is required to move the company's request forward?

The New Drug Application (NDA) for the sponge remains active; however, Allendale Pharmaceuticals must submit two supplements for FDA approval. One supplement is for the product label, which has been submitted to the FDA for its review, says Staab. The second supplement is to change the manufacturing plant to the OSG Norwich site.

According to Staab, the company has product stability material ready for the FDA's review, which is scheduled for this month. The FDA also may elect to perform a preapproval inspection for manufacturing compliance at the OSG Norwich site, which has an "excellent" compliance record, he reports.

### *Examine the sponge*

The Today Sponge is circular in shape, two inches in diameter, and three-quarters of an inch thick, with an attached loop. Made of polyurethane, it contains 1,000 mg of the spermicide nonoxynol-9 (N-9). It is moistened with tap water prior to use and inserted deep into the vagina; removal is achieved by pulling the attached loop.

The sponge protects for up to 24 hours, no matter how many times intercourse occurs. According to the company's product information, the Today sponge should not be left in place for more than 30 hours after insertion (which includes the six-hour waiting period

after the last act of intercourse). It should not be used during menstruation; immediately after childbirth, miscarriage, or other termination of pregnancy; or by women who have ever been diagnosed with toxic shock syndrome. Women using the sponge who experience two or more of the warning signs or symptoms of toxic shock syndrome — including fever, vomiting, diarrhea, muscular pain, dizziness, or rash similar to sunburn — are advised to contact a physician immediately.

The advantages of the sponge are that it is simple to use and noninvasive, and it can be used intermittently with little advance planning.[3]

Unlike the diaphragm, the sponge can be used for more than one coital act within 24 hours without the insertion of additional spermicide, and it does not require fitting or a prescription from a health care provider.[4]

In the array of available contraceptive options, the sponge falls below the diaphragm in contraceptive effectiveness. In a recent review of available data, the sponge statistically was significantly less effective in preventing overall pregnancy than was the diaphragm in the two trials that met analysts' inclusion criteria, one performed in the United States[5] and one in the United Kingdom.[6] The 12-month cumulative life table termination rates per 100 women for overall pregnancy were 17.4 for the sponge vs. 12.8 for the diaphragm in the U.S. trial, and 24.5 for the sponge and 10.9 for the diaphragm in the UK trial. Discontinuation rates at 12 months were higher with the sponge than with the diaphragm.[4]

Allergic reactions were more common with the sponge in both trials, although the frequency of discontinuation for discomfort differed in the two studies. In the U.S. trial, the 12-month cumulative life-table discontinuation rate for allergic reactions per 100 women were 4.0 for the sponge, vs. 0.7 for the diaphragm. The corresponding figures from the British trial were 0.9 and 0.0. Allergic-type complaints included dermatitis, erythema, and irritation, with vaginal itching as the chief discomfort-related complaint.[4]

## Alternate agent on tap?

While early research indicated that the N-9 contained in the sponge may reduce the risk of some sexually transmitted diseases (STDs),[7,8] more recent research suggests that effect is unlikely.[9,10] The FDA has proposed labeling changes for all vaginal contraceptives containing N-9 to help users understand that the use of such products can increase vaginal irritation, which actually may heighten the possibility of acquiring the AIDS virus and other STDs from infected partners. **(Review the FDA's proposed revisions in the article, "Labeling change: New warning proposed for nonoxynol-9 contraceptive drugs," *CTU*, March 2003, p. 25.)**

The formulation for the current sponge is exactly the same as that was approved in the original NDA; Allendale Pharmaceuticals cannot change it, says Staab.

The company is looking at alternative spermicides/microbicides for the Sponge format, he says. To make such a change, the company would have to go through the full regulatory process to ensure the safety and efficacy of the product, which would be a "big project," Staab notes.

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# The Pill for PMS relief? New research says yes

Your next patient says she has breast tenderness, headaches, bloating, and weight gain during the luteal phase of her menstrual cycle, which indicates premenstrual syndrome (PMS). What is your next move?

New research indicates that use of the oral contraceptive (OC) Yasmin decreased the physical and emotional symptoms associated with a woman's menstrual cycle.[1] "We have ongoing clinical trials right now for a different dose of Yasmin in premenstrual dysphoric disorder (PMDD), which is a more severe form of PMS," reports **Kim Schillace**, company spokeswoman for the drug's manufacturer, Berlex Laboratories of Montville, NJ. "We will seek that indication if the data come back in a positive way."

The company is examining use of a lower dose of the currently available oral contraceptive (3 mg drospirenone and 0.030 mg ethinyl estradiol), states Schillace. **(See the *Contraceptive Technology Update* article, "Oral contraceptive with unique progestin receives FDA approval," July 2001, p. 73, for news of the OC's regulatory approval, and the *Contraceptive Technology Reports*, "Evaluation of a new oral contraceptive progestogen drospirenone with ethinyl estradiol," inserted in the September 2001 issue, for a clinical review of the drug.)**

## Look at the results

In the latest published research, scientists tracked and scored the physical, behavioral, and emotional symptoms of PMS reported by women at three phases of their menstrual cycle and before and after use of Yasmin.

Study participants reported being better able to perform daily activities after beginning therapy and said their general sense of well-being improved during their menstrual cycle.

After starting use of the drug, the number of women reporting that PMS affected their daily activities moderately, quite a bit, or extremely was reduced from 30% to 16% of participants. Similarly, the number of study participants reporting that PMS affected their general well-being moderately to extremely dropped from 35% to 21% following use of the drug therapy.

In new oral contraceptive users, researchers noted improvements in symptoms during the four days before the period and during menstruation, including those associated with water retention (weight gain, skin disorders, painful breasts, and swelling), as well as those in the negative affect cluster (crying, loneliness, anxiety, restlessness, irritability, mood swings, depression, tension, and food cravings). For these patients, the improvement in negative affect also extended into the remainder of the cycle, except crying and loneliness. For patients who had switched to Yasmin from other oral contraceptives, improvements were noted for all phases of the cycle.

Yasmin's progestin may be the key to the drug's impact on PMS symptoms, theorizes **Andrea Rapkin**, MD, study author and professor of obstetrics and gynecology at the University of California, Los Angeles.

The progestins used in other combined oral contraceptives are derived from testosterone, she explains. While chemically different, they still may retain androgenic properties, which may result in weight gain and appetite increase.

"This particular pill is derived from a chemical which is related to spironolactone, which is a diuretic and an anti-androgenic compound," states Rapkin. "It is progestogenic, which you need for birth control, but at the same time, it has other properties that would suggest that you would have fewer side effects and better quality of life with this pill."

## What is PMDD?

Make the distinction between PMS and PMDD when evaluating patients' symptoms. To diagnose PMDD, symptoms must occur during the week preceding menses and remit several days after the

### EXECUTIVE SUMMARY

Findings from a recent study show that Yasmin, an oral contraceptive (OC) with an ethinyl estradiol and drospirenone combination, offered relief from the physical and emotional symptoms associated with premenstrual syndrome (PMS).

- Berlex Laboratories, which markets the OC, is researching the potential use of the pill in treatment of premenstrual dysphoric disorder, the more severe form of PMS.
- The drug's unique progestin may be the key to the drug's impact on PMS symptoms; researchers continue to analyze the drug's effectiveness for the proposed indication.

onset of menstruation. Symptoms may include five of the following: markedly depressed mood, anxiety or tension, affective lability, anger or increased irritability resulting in increased interpersonal conflicts, decreased interest in usual activities, difficulty concentrating, lethargy or easy fatigability, changes in appetite, sleep disturbances (hypersomnia or insomnia), and a feeling of being overwhelmed, plus physical symptoms such as breast tenderness, headaches, joint/muscle pain, bloating, or weight gain.[2] **(The article, "Clinical quandary: Is it PMS or PMDD? Find answer by listening to patients," *CTU*, April 2001, p. 37, carries a complete overview of PMS, PMDD, and treatments.)**

Selective serotonin reuptake inhibitors (SSRIs), such as Sarafem (fluoxetine, Eli Lilly & Co., Indianapolis) have been effective in treating PMDD, notes Rapkin. However, side effects such as nausea, dry mouth, decreased libido, and insomnia have been problematic for some patients. Research into other drugs would afford more treatment options, she notes.

"We know that there seems to be some relationship with the syndrome and serotonin, so other medications which alter seratonergic profile without the side effects of SSRIs, for example, might be very helpful," Rapkin comments. "In addition, the concept of using a contraceptive pill continuously rather than cyclically, where you don't have the small cycles of hormone fluctuation that you have with the cyclic pill, also might be useful." **(Dutch medical officials have raised safety concerns about Yasmin and risk of venous thromboembolism; see the below story.)**

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# Yasmin is the focus of Dutch safety alert

While the oral contraceptive (OC)Yasmin (Berlex Laboratories, Montville, NJ) has been the focus of interest in the United States for its potential in treating premenstrual syndrome, its safety has been questioned by Dutch medical officials, who are calling for more epidemiological data on the potential risk for venous thrombosis.

The Amsterdam-based Dutch College of General Practitioners issued a warning about the pill following the death of a 17-year-old female who was using the OC.[1] The Dutch medicines evaluation board, which monitors adverse drug reactions in the country, recently received five reports of thromboembolism in connection with use of the drug.[2]

Yasmin has been licensed in Europe since November 2000. Schering AG of Berlin, Germany, Berlex Laboratories' parent company, estimates that about 35,000 women in the Netherlands are using the pill, joined by 500,000 women in 17 European countries. Yasmin was approved by the Food and Drug Administration in 2001, and it entered the British market in 2002.

The risk of venous thromboembolism (VTE) associated with pill use has been of particular interest in Europe since 1995, when study findings suggested a higher risk among users of third-generation OCs compared to those on second-generation pills.[3,4,5] **(See the *Contraceptive Technology Update* article, "British pill scare leaves American women unfazed," January 1996, p. 6, for an overview of the origins of what has been dubbed the "pill scare," which arose following a warning from British medical officials on the use of OCs containing gestodene and desogestrel.)**

The progestin in Yasmin is different from other pills; it is synthesized from 17 alpha spironolactone. According to the Dutch Medicines Evaluation Agency, some clinicians had been choosing the drug over second- and third-generation pills under the assumption that the risk of VTE would be less than other pills; however, such a conclusion cannot be reached from the available data, it stated.[1]

Yasmin's manufacturers stand by the safety of the drug, says **Kim Schillace**, Berlex Laboratories spokeswoman. The company has monitored drug use since the OC was launched, and its data indicate there is no difference between Yasmin and any other oral contraceptive with respect to the risk of VTE, she states. Interim results from Schering's post-marketing surveillance study of a million cycles show that, after one year, one venous thrombosis occurred among Yasmin users, compared with five among users of other oral contraceptives.[1]

All oral contraceptives and estrogen-containing products carry a labeled risk of venous thrombosis, Schillace notes. Health care providers and patients need to review the risks and benefits when women are considering use of these products, she states.

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# Menstruation on hold? More women favor option

**EXECUTIVE SUMMARY**

New research indicates that many women prefer to menstruate less often. In an international survey, most women said they disliked periods due to their inconvenience.

- Most women surveyed said they would opt to bleed once every three months or not at all, and they said they would be willing to try a contraceptive that induces amenorrhea.
- Clinicians can offer several options for safe, effective birth control with reduced uterine bleeding, including extended use of combined oral contraceptives, progestin-only contraceptive injections, and the levonorgestrel intrauterine system.

Ask your next patient if she would like to reduce the number of bleeding days requiring sanitary protection as well as lessen such troublesome symptoms as bloating and cramps. Chances are that she will say "yes."

"Interest continues to grow among clinicians and women regarding using hormones to reduce menstruation," says **Andrew Kaunitz**, MD, professor and assistant chair in the obstetrics and gynecology department at the University of Florida Health Science Center/Jacksonville. **(See the *Contraceptive Technology Update* January 2002 article, "Research eyes extending the menstrual cycle," p. 3, for further information surrounding menstrual suppression.)**

While surveys conducted in the 1970s and 1980s suggested that amenorrhea was unacceptable to most women, more recent research indicates that more women prefer to menstruate less often.[1] Scientists recently conducted an international survey to explore women's willingness to use a contraceptive that induces amenorrhea.[1]

The study, which analyzed responses from a questionnaire survey of 1,001 women attending family planning clinics and 290 contraceptive providers in China, South Africa, Nigeria, and Scotland, found that most women disliked periods, which they termed "inconvenient."[1] Only among black women in Africa did the majority like having periods. Given the choice, the majority of Nigerian women said they would prefer to bleed monthly; elsewhere, women said they would opt to bleed only once every three months, or not at all. The Nigerian women said they liked having periods to "get rid of bad blood" and to reassure themselves that they were not pregnant. The majority of women surveyed said they would be willing to try a contraceptive that induces amenorrhea.

Reduced bloating and menstrual pain may be desirable options for women who choose continuous oral contraceptive (OC) dosing regimens, according to another recent study.[2] Scientists compared bleeding patterns and acceptability of a contraceptive regimen of a combined 20-mcg ethinyl estradiol/100-mcg levonorgestrel pill from Wyeth Pharmaceuticals of Collegetown, PA, taken with and without a hormone-free interval.[2] In this small study, women were randomized to six conventional cycles (21 days of active tablets followed by seven hormone-free days) or 168 continuous days of active tablets. Outcomes assessed included bleeding (flow requiring sanitary protection), spotting (no protection), headache, nausea, bloating, breast tenderness, premenstrual syndrome, and menstrual pain.

Although both groups reported a high level of satisfaction with bleeding patterns and side-effect profiles, women in the continuous group reported significantly fewer days of bloating and menstrual pain.

### Examine the options

Women have options outside extended use of combined OCs when it comes to safe, effective birth control with reduced uterine bleeding, says

Kaunitz. These include the Depo-Provera contraceptive injection (depot medroxyprogesterone acetate, Pharmacia Corp., Peapack, NJ) and the Mirena levonorgestrel intrauterine system (Berlex Laboratories, Montville, NJ). Researchers also are looking at extended use of the contraceptive patch (Evra, Ortho McNeil Pharmaceuticals, Raritan, NJ) and ring (NuvaRing, Organon, West Orange, NJ) as potential candidates for reducing menstruation.

According to *A Pocket Guide to Managing Contraception*, women whose quality of life would be improved by reducing the frequency of or eliminating menses with continuous OC use may include women who are on military assignment or women with cyclic depression, headaches, or premenstrual syndrome.[3] Use monophasic pills when prescribing a continuous-use regimen, it suggests.

### Seasonale under review

An oral contraceptive with a regimen specifically designed to put menstruation on hold is under evaluation by the Food and Drug Administration (FDA) The agency accepted Pomona, NY-based Barr Laboratories' New Drug Application for its proprietary pill, Seasonale, in August 2002; the company continues to work with the FDA on the application, say company officials.

Barr Laboratories, in agreement with the Medical College of Hampton Roads, Eastern Virginia Medical School in Norfolk, VA, are developing the pill. **(*CTU* reported on Seasonale in the May 1999 article, "4-periods-per-year pill eyed for use in U.S. market," p. 51, and the August 2002 article, "4-periods-per-year OC: Comparable to pill," p. 87.)**

The Seasonale regimen is designed to reduce the number of withdrawal bleeds from 13 to four per year. Under its regimen, women take the OC for up to 84 consecutive days, followed by seven days of placebo. This pill-taking regimen contrasts with the majority of oral contraceptives, which are based on a regimen of 21 treatment days, followed by seven days of placebo.

In a multicenter trial, two versions of the Seasonale extended oral contraceptive therapy prevented pregnancy comparable to study drugs.[4] The adverse profile of the Seasonale drug was similar to that of other oral contraceptives, study findings indicate.

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# No link found between abortion, breast cancer

Epidemiological evidence presented at a recent Bethesda, MD-based National Cancer Institute (NCI) workshop could help end a longstanding debate on the question of induced abortion and risk of breast cancer.

"Our studies did not find breast cancer risk to be increased overall or in any subgroups of women, defined by age at the time of the abortion or by length of gestation when the abortion occurred," states **Leslie Bernstein**, PhD, senior associate dean at the University of Southern California in Los Angeles, who presented information at the workshop. "Concern had been expressed previously regarding some subgroups defined by age and gestational length."

Outcomes of the meeting were reviewed by the NCI's Board of Scientific Advisors and Board of Scientific Counselors, which has since issued a report summarizing the epidemiologic, clinical,

**EXECUTIVE SUMMARY**

A scientific panel at the National Cancer Institute (NCI) has concluded there is no evidence that an abortion increases the risk of breast cancer later.

- Dissension arose following the posting of a revised fact sheet on the NCI web site. The fact sheet had stated that studies showed "no association between abortion and breast cancer"; however, it was revised to state the evidence was inconclusive.
- Researchers recently presented findings from three large studies showing no increase in breast cancer risk associated with abortion. Scientists also offered extended results from an earlier study of 1.5 million Danish women, which also showed no overall effect.

and animal studies findings related to early reproductive events and breast cancer risk. According to the report, the evidence showing that induced abortion is not associated with an increase in breast cancer risk is well established.[1]

The workshop was convened after dissension arose following the posting of a revised fact sheet on the NCI web site, www.cancer.gov. The federal agency, which offers information on cancer detection, prevention, and treatments for consumers and health professionals, first developed a fact sheet on the question of abortion and breast cancer in October 1994.[2] The fact sheet, which has been revised six times, had stated that studies showed "no association between abortion and breast cancer." In November 2002, however, the fact sheet was revised to state the evidence for a link between induced abortions and breast cancer was inconclusive.[3]

A new fact sheet containing the workshop's findings had just been posted, says **Mary Anne Bright**, acting deputy director of the NCI office of communications. **(Access the fact sheet on-line at the NCI web site. Click on "Early Reproductive Events and Breast Cancer," then "Abortion, Miscarriage, and Breast Cancer Risk Factor Fact Sheet.")**

## Review the evidence

Why have some researchers linked abortion with an increased risk for breast cancer? According to information from the New York City-based Planned Parenthood Federation of America, such a belief has been linked to the hormonal disruption that occurs when a woman's pregnancy is terminated. Some researchers have claimed that interruption of the first trimester of a first pregnancy causes a cessation of cell differentiation that may result in a subsequent increase in the risk of cancerous growth in these tissues; attempts to prove this theory, however, have failed.

At the February 2003 workshop, participants reviewed evidence on all aspects of pregnancy in relation to breast cancer risk. Bernstein presented new data from three large studies showing no increase in breast cancer risk in association with having an abortion. Two of the studies are unpublished; one has just been published in the journal *Cancer Epidemiology Biomarkers & Prevention*.[5]

The studies did not find breast cancer risk to be increased overall or in any subgroups of women, defined by age at the time of the abortion or by length of gestation when the abortion occurred, says Bernstein. Concern had been expressed previously regarding some subgroups defined by age and gestational length, she notes.

An important issue in the statistical analysis of such studies is whether women who have never had a term pregnancy but have been pregnant are compared to women who have had term pregnancies, observes Bernstein. Such an approach does not address the question, "does an induced abortion increase breast cancer risk?" and could lead to incorrect conclusions, she notes.

"In our analyses, we assessed whether biased reporting might have occurred; we found no evidence of any underreporting of an induced abortion by women who served as controls in the two case-control studies," states Bernstein. "Such underreporting generally leads to elevated estimates of breast cancer risk when none actually exists, and this is a likely explanation for some of the studies in which an association was reported."

Additional data were presented in the closed session of the workshop, which extended results from an earlier study of 1.5 million Danish women.[6] The original study showed no overall effect on the risk of breast cancer and induced abortion; the follow-up evidence strengthened the original findings, says Bernstein.

Following the presentations, scientists discussed the state of the evidence, crafted statements regarding the evidence, and assigned the statements a numeric code that indicated the level of certainty, says Bernstein. It was concluded that induced abortion is not associated with an increased risk of breast cancer, she notes.

## Other findings eyed

The panel also accepted several other findings, including the following:

- Early age at first-term birth is related to lifetime decrease in breast cancer risk.
- Increasing parity is associated with a long-term risk reduction, even when controlling for age at first birth.
- The additional long-term protective effect of young age at subsequent term pregnancies is not as strong as for the first-term pregnancy.
- Breast cancer risk is transiently increased after a term pregnancy.
- Recognized spontaneous abortion is not associated with an increase in breast cancer risk.
- Long duration of lactation provides a small additional reduction in breast cancer risk after consideration of age at and number of term pregnancies.

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ASK THE EXPERTS

# Questions on Pap smears and pills? Look no further

What is your approach when it comes to oral contraceptives and women who smoke? What is your facility's standard practice for informing patients on Pap test results?

The following members of *Contraceptive Technology Update*'s Editorial Advisory Board share their insights on these questions: **David Archer**, MD, professor of obstetrics and gynecology and director of the Clinical Research Center at the Eastern Virginia Medical Center in Norfolk; **Linda Dominguez**, RNC, NP, assistant medical director of the Albuquerque-based Planned Parenthood of New Mexico; **Michael Rosenberg**, MD, MPH, clinical professor of obstetrics and gynecology and adjunct professor of epidemiology at the University of North Carolina at Chapel Hill and president of Health Decisions, a private research firm specializing in reproductive health; **Sharon Schnare**, RN, FNP, CNM, MSN, women's health consultant and clinician with the Seattle King County Health Department in women's and adolescent health care and the International District Community Health Center in Seattle; and **Susan Wysocki**, RNC, NP, president and chief executive officer of the Washington, DC-based National Association of Nurse Practitioners in Women's Health.

**Question:** Do you think women who smoke and take oral contraceptives (OCs) should be counseled on the potential for breakthrough bleeding (BTB)? If so, how much smoking is enough to potentially cause a problem?

**Archer:** I think that it is important to emphasis that smoking may increase the risk for breakthrough bleeding. The data from Rosenberg's article support this.[1] The clinical information is limited, but I think that it is significant.

**Dominguez:** I have found the amount of smoking impacting BTB is variable but a real contributor to this side effect. What is most important is that the clinician should not discount that the smoking is an often-overlooked reason for the problem of breakthrough bleeding and spotting. This is important because these unpredictable symptoms of unscheduled bleeding are a leading cause for patients to self-discontinue or for pill prescription changes by the clinician.

**Rosenberg:** Although there is very little research on the subject, smoking has an anti-estrogenic effect — probably by increasing the breakdown of estrogen and metabolites — and acts to effectively reduce the estrogen in OCs. Smoking has clearly been indicated in one investigation as an independent risk factor for spotting and breakthrough bleeding.[1] I do regard smokers at being at increased risk for cycle control problems and recommend counseling.

**Schnare:** According to Speroff and Darney, smoking is associated with BTB.[2] The authors cite the following study.[3] I tell patients that their smoking may affect BTB. I also discuss smoking cessation with all women who smoke, and I let women know that the combined OCs are contraindicated once she turns 35 years of age. It's also important to remind ourselves and our patients that women younger than 35 years who smoke and use combined OCs are also at greater risk of myocardial infarction when compared to nonsmoking women using combined pills.

**Question:** Is it legally necessary to notify a patient of the results of a "normal" Pap smear? As a nurse practitioner, in other clinics where I have worked, we notified all patients of the results of their Pap tests even if they were normal. Where I am at this time, we do not notify

patient of "normal" results except by the statement at the time of the exam, "If your test is abnormal, we will call you. If it is normal, you won't hear from us."

**Archer:** I am not sure about legality. I do believe that we should notify our patients in writing of the interpretation of their Pap smear. At present, the ASCUS [atypical squamous cells of undetermined significance] issue looms large, and I think that something in writing helps the patient, who may opt to go elsewhere for a second opinion. No answer implying normal findings does not seem appropriate today.

**Schnare:** I am not an attorney. I have worked in institutions where normal findings were not reported to women, and women were told that if their Pap smears were normal, they would not be called. I think this may be the standard of care in many institutions. I also have worked in the private sector where all women were informed of results by phone or letter, no matter what their Pap results were. My sense is that, as long as an institution has written procedures regarding Pap reporting to women and as long as the institution follows its own procedures, there should be no greater legal risk of not reporting normal results; of course, women should be told this is the policy.

**Wysocki:** There is no legal responsibility to notify a patient of normal Pap results, although many practices do notify patients. Your medical legal responsibility is to ensure that the Pap test taken that day is sent out, read, results returned to the practice, and recorded in the patient's chart. There should be tracking systems in place, such as a log, to see that every Pap taken is sent out and returned.

If the results are anything less than "normal," the results should be compared to test results in the past. A series of low-grade Paps may be as important as a single high-grade reading. Results of Paps that are anything but normal should be shared with the patient.

*(Editor's note: Take a look at your facility's practices to see that the following four elements are addressed when it comes to test results management: tracking tests until the results have been received; notifying patients of the results; documenting that the notification occurred; and making sure that patients with abnormal results receive the recommended follow-up care.[4])*

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# Family planning cited for counseling efforts


By **Cynthia Dailard**
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Washington, DC


Without fanfare, the Bush administration has issued an important report to Congress on nondirective pregnancy options counseling in family planning clinics. Specifically, the report sought to assess the extent to which adoption information and referral is provided as part of nondirective counseling in publicly funded clinics.

The report reviews the professional standard of care for counseling pregnant women. It summarizes conversations with nine individuals noted for their expertise in relevant fields and includes interviews with 14 clinicians working in community health centers and/or Title X family planning clinics.

This report was mandated by the "Infant Adoption Awareness Act of 2000." That legislation funds training for family planning providers, including Title X providers, on how to provide adoption information and referral on par with other options in nondirective pregnancy options counseling. Former Rep. Tom Bliley (R-VA), a staunch family planning opponent, authored the law.

Despite the report's genesis, it is extremely favorable to family planning providers and is likely to put to rest the likelihood that the administration or members of Congress hostile to the Title X program will attempt to revive the domestic family planning gag rule. First and foremost,

it acknowledges that nondirective options counseling that includes information about all of a woman's options, *including abortion,* is uniformly recognized as the standard of care in federal programs and by professional organizations.

### *The experts agree*

The experts consulted, moreover, were uniform in their understanding of nondirective counseling. They explained that nondirective counseling is more prevalent in federally funded family planning clinics than in the private sector, in part because patient education is more likely to be emphasized by the public sector and because public sector programs are held to high levels of public accountability. They emphasized that Title X providers are trained extensively in this area and that additional Title X funding would help clinics to further enhance their counseling efforts.

At the same time, the experts noted that clinicians sometimes perceive that local adoption agencies are biased against Title X clients: A "shared sentiment [among the experts consulted] was that local adoption agencies have been perceived by clinicians as sending a message to clinics treating poor women — in particular, women of color with high health risks — that their infants are not desirable and that an adoption referral is not warranted," and that some adoption agencies "have been less than enthusiastic about the referrals that come from public clinics."

Clinician interviews confirmed that they receive extensive training in nondirective counseling, which includes training on adoption information and referral. They indicated, however, that most women usually know what they want to do regarding their pregnancy before coming to the clinic. Adoption is not a popular choice among their clients, they explain, in part because adoption is frowned upon by some of the communities served by family planning clinics; children from these cultures tend to be "informally adopted" by a grandparent or other relative. The clinicians suggested that local adoption agencies needed to become more culturally sensitive to the clinic's patient population. Some clinicians indicated that they would be interested in receiving further information on adoption "to help explain the complicated legal, confidentiality, and family issues related to the adoption process."

The report concludes that federally funded family planning providers "are expected to adhere to the general professional standard, not only as a condition of grant award, but as a basic matter of clinical and professional ethics" and that "infant adoption as part of nondirective counseling to pregnant women is an accepted and adhered-to standard among clinicians at federally funded health clinics." However, it notes that where the adoption agency in a community is perceived as culturally insensitive, "the tendency may be to avoid bringing up the subject"; this, the report says, must be addressed in federally funded training programs. Finally, the report says that further research is needed to study clinical settings where there are strong relationships between health providers and adoption agencies, and that such efforts should be replicated. ■

## 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 issue, you must complete the evaluation form provided in the June issue 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*

- The Pill and breast cancer — Are there risks?
- Review new data on hormone therapy
- Get comprehensive data on HIV/AIDS
- Check out contraception for spacing births
- Birth control options for hypertensives

# CE/CME Questions

*For more information about the CE/CME program, contact customer service at (800) 688-2421, or e-mail customerservice@ahcpub.com.*

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

- Identify clinical, legal, or scientific issues related to development and provision of contraceptive technology or other reproductive services. **(See "Time for Today sponge in Canada — will U.S. see vaginal contraceptive?" "The Pill for PMS relief? New research says yes," "Menstruation on hold? More women favor option," and "Herpes numbers rise — you must know your options" in this issue.)**
- Describe how those issues affect service delivery and note the benefits or problems created in patient care in the participant's practice area.
- Cite practical solutions to problems and integrate information into daily practices, according to advice from nationally recognized family planning experts.

17. What is the active spermicide found in the Today contraceptive sponge?

A. Octoxynol-9
B. Menfegol
C. Chlorhexidine gluconate
D. Nonoxynol-9

18. Which class of drugs has been shown effective in treating premenstrual dysphoric disorder?

A. Selective serotonin reuptake inhibitors
B. Angiogenesis inhibitors
C. Fusion inhibitors
D. Endothelin receptor antagonists

19. According to a new international study (Glasier AF, et al. *Contraception* 2003; 67:1-8), what was the preferred bleeding pattern preferred by the majority of women surveyed?

A. Once a month
B. Once every four months
C. Once every three months, or not at all
D. Once every six months

20. What are the three drugs available for treatment of genital herpes?

A. Acyclovir, famciclovir, valacyclovir
B. Acyclovir, ceftriaxone, valacyclovir
C. Acyclovir, famciclovir, cefixime
D. Penicillin, famciclovir, valacyclovir

**Answer key: 17. D; 18. A; 19. C; 20. A.**




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S·T·D QUARTERLY™

# World's first large-scale HIV vaccine trial doesn't indicate protection for overall population

*Scientists won't give up on their hunt for effective vaccine*

The news is in from the world's first large-scale trial of a HIV vaccine, and it isn't good: The vaccine failed to achieve a statistically significant reduction of HIV infection within its study population as a whole.

While scientists are debating the analysis of findings from the AIDSVAX B/B vaccine trial, they do agree on one thing: the search must go on to find an effective HIV vaccine. Worldwide, an estimated 5 million people were newly infected with HIV in 2001.[1]

"AIDSVAX was important because it demonstrated for the first time that we are able to conduct a scientifically sound Phase III trial on a global basis," observes **Lawrence Corey**, MD, principal investigator of the Seattle-based HIV Vaccine Trials Network (HVTN), a partnership of research scientists, clinical trial sites, and community representatives working with industry and governments in the global HIV vaccine search. "The next step is to continue pressing forward with Phase I and II trials so that scientists can identify the best vaccine candidates to take to Phase III."

In the landmark first trial, 3,330 volunteers received the AIDSVAX B/B vaccine, and 1,679 received a placebo. According to the initial results, the percentage of volunteers who received AIDSVAX and became infected with HIV is statistically equal to the percentage of volunteers who received the placebo and became infected with HIV, meaning that the vaccine is not protective for the overall population.

However, the study did show a statistically significant reduction of HIV infection in certain vaccinated groups, claims VaxGen of Brisbane, CA, the developer of the AIDSVAX vaccine. The results are the first to be reported from the company's three-year, multinational, randomized, double-blind, placebo-controlled Phase III trials of AIDSVAX. **(*Contraceptive Technology Update* reported on HIV vaccine research in its *STD Quarterly* article, "HIV vaccines: New generation may reduce transmission of virus," inserted in the October 2002 issue.)**

Initial results from the trial, which tested the AIDSVAX B/B vaccine, yielded the following

## EXECUTIVE SUMMARY

Preliminary results from the world's first large-scale clinical trial show the AIDSVAX B/B vaccine does not provide HIV protection for the overall population.

- Initial results show the vaccine failed to achieve a statistically significant reduction of infection within its study population as a whole. However, the vaccine did show a statistically significant reduction of infection in certain vaccinated groups, claims its manufacturer. Some scientists question if such subgroup findings are statistically relevant.
- The National Institute of Allergy and Infectious Diseases is working on more than 20 vaccine candidates.

preliminary findings:

• The reduction of infection among the entire sample of volunteers, including all racial groups, was 3.8% (p-value = 0.76; n = 5,009).

• There were 67% fewer HIV infections among ethnic minorities, other than Hispanic individuals, who received vaccine compared to placebo recipients (p-value <0.01; n = 498).

• There were 78% fewer HIV infections among black volunteers who received vaccine compared to placebo recipients (p-value <0.02; n = 314).

Some scientists question whether the analysis of the AIDSVAX subgroup findings can be statistically significant due to the low numbers of participants within the subgroups. What is the company's next move?

"VaxGen's next steps are to finish our analyses by merging our clinical and laboratory data in an effort to find a biological explanation for the efficacy we saw in some subgroups," says company spokesman **Jim Key**. At press time, a more detailed analysis of the data was set to be presented at the Keystone Symposia on HIV, scheduled for March 29 to April 4 in Banff, Alberta.

## Thailand results next

The AIDSVAX vaccine is composed of a recombinant form of the protein (gp120) on the surface of HIV and is produced in mammalian cell culture. The vaccine contains noninfectious, genetically engineered proteins (rgp120) that mimic proteins on the surface of two strains of HIV subtype B. Subtype B is prevalent in North America, Europe, Australia, Japan, and Puerto Rico.

The AIDSVAX B/B trial, conducted in the United States, Canada, Puerto Rico, and the Netherlands, included 5,108 men who have sex with men and 309 at-risk women, all of whom tested HIV-negative when they joined the trial. Three shots, spaced three months apart, were given initially, followed by booster shots every six months. All volunteers were counseled to practice safer sex and not to count on protection from the vaccine.

VaxGen's Phase III trial in Thailand is testing a formulation of AIDSVAX designed to protect against HIV subtypes B and E, which is prevalent in Southeast and East Asia and the Central African Republic. The trial is to be completed soon, says Key. The company will announce the results of that trial in the second half of 2003, he notes. Unlike the AIDSVAX B/B trial, which tested the vaccine against sexual transmission of the virus, the trial in Thailand is examining the vaccine's effectiveness against infection acquired by injection drug use. ***(CTU* will report the results of the Thailand trial when the study is completed.)**

VaxGen scientists are in the early stage of developing a vaccine against HIV subtype C, prevalent in Sub-Saharan Africa, India, and China. The company is committed to developing increasingly effective formulations of AIDSVAX that target all HIV subtypes.

## New approaches in wings

Look to the future for important news on vaccine research. The Bethesda, MD-based National Institute of Allergy and Infectious Diseases (NIAID) is aiding in the development of more than 20 vaccine candidates to prevent HIV infection. Some vaccines are in the early stages of preclinical evaluation, while others are near testing in human subjects. Several new types of HIV vaccines are under investigation, with ongoing trials of adenovirus and canarypox vectors as well as DNA-based vaccines.

Six to eight new clinical trials will move these products forward in safety evaluations in the next 12-18 months, according to the HVTN, which is funded by NIAID. Additional research is being conducted in NIAID's Dale and Betty Bumpers Vaccine Research Center in Bethesda.

Clinical tests began in November 2002 of a novel vaccine directed at the three most globally important HIV subtypes, or clades. The vaccine, developed by scientists at the NIAID's research center, incorporates HIV genetic material from clades A, B and C, which cause nearly 90% of all HIV infections around the world. It is the first multigene, multiclade HIV vaccine to enter human trials, according to the NIAID.[2]

The vaccine includes parts of four HIV genes; three of these vaccine components are modified versions of HIV genes called *gag, pol,* and *nef* taken from clade B, the subtype that predominates in Europe and North America. The fourth vaccine component is derived from an HIV gene, *env*. According to NIAID scientists, the *env* gene codes for a protein on the outer coat of the virus that allows it to recognize and attach to human cells. The vaccine represents the first attempt to combine modified *env* from clades A and C,

which are the most common in Africa, as well as from clade B. A single vaccine combining multiple *env* components from different HIV subtypes could be effective in many places in the world, states the NIAID.

Another Phase I trial includes an experimental vaccine developed by the Yerkes National Primate Research Center of the Atlanta-based Emory University, the university's Vaccine Center, and the Bethesda-based NIAID Laboratory of Viral Diseases.[3] The vaccine strategy includes two inoculations of a DNA vaccine that primes the immune system to recognize HIV, and a subsequent booster vaccine based on a recombinant poxvirus. Neither of the components incorporates the actual virus; instead, the vaccine produces the three major proteins expressed by HIV. Scientists believe the vaccine induces the immune system to respond to the distinguishing features of HIV so the system will respond to the actual virus should it appear.

"The HIV Vaccine Trials Network has four Phase I and II trials under way now, with four more beginning shortly," Corey remarks. "Trials like these are essential to finding an effective, global HIV vaccine."

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# Herpes numbers rise — you must know your options


**EXECUTIVE SUMMARY**

The number of genital herpes infections continues to swell. One out of five of the U.S. adolescent and adult population is infected with herpes simplex virus type 2.

- Research of an experimental drug has been suspended since preliminary data showed it was not as effective as expected. The companies involved with the drug, resiquimod, are evaluating results of previous tests to determine further exploration.
- Three drugs are available for herpes treatment: acyclovir, famciclovir, and valacyclovir. Clinicians can use these drugs in episodic therapy, which speeds healing when outbreaks occur, or suppressive therapy, to reduce the number and severity of outbreaks.


It's back to the research drawing board in the search for more treatment options for genital herpes. A clinical trial of an experimental drug, resiquimod, has been suspended since preliminary data showed it was not as effective as expected.

Clinicians need more tools to fight the swell of genital herpes infections. According to the Atlanta-based Centers for Disease Control and Prevention (CDC), 45 million Americans ages 12 and older, or one out of five of the total adolescent and adult population, are infected with the herpes simplex virus-2 (HSV-2).[1] Since the late 1970s, the number of Americans with genital herpes infection has increased 30%, with the largest increase occurring in young white teens. HSV-2 infection is now five times more common in 12- to 19-year-old whites, and it is twice as common in young adults ages 20-29 than it was 20 years ago, says the CDC.[1]

The two companies involved in the research of resiquimod, Eli Lilly & Co. of Indianapolis and 3M Pharmaceuticals of St. Paul, MN, are evaluating the recent Phase III trials results and the more positive results seen in earlier Phase II trials to determine whether to conduct additional clinical trials of resiquimod for the treatment of genital herpes, says **Terra Fox**, Eli Lilly spokeswoman. It is premature to comment on the timing of determining whether the companies will pursue further research of the drug as a potential treatment for the sexually transmitted disease (STD), says Fox.

Initial research of the drug, part of a new class of drugs known as immune response modifiers, had been promising. Results of a pilot study indicated that application of resiquimod to genital herpes lesions appeared to reduce the frequency of recurrences.[2] In that study, 52 patients were randomized to receive the drug in one of four dosing regimens. Patients, whose ages ranged from 18 to 60, had a history of recurrent genital herpes, with an average of 10 episodes per year. Patients

applied the drug within 24 hours of the onset of symptoms for three weeks and were observed for six months after treatment. The median time to recurrence was 57 days for patients treated with vehicle alone vs. 169 days for those who received the drug. Patients who received placebo had a median of 5.5 recurrences during the six-month observation period, compared with one recurrence among those who received resiquimod.[3]

In the study, scientists noted that the delay to develop the next herpes lesion recurrence continued long after applications of the topical gel ended, which suggested that the treatment is similar to a vaccination, prompting levels of interferon a, interleukin 12, and other cytokines that boost cell-mediated immunity.

## Three options available

Herpes is not curable, but it can be managed with antiviral medications that are used in episodic therapy, which speeds healing when outbreaks occur, or suppressive therapy, where drugs are taken as a preventive measure to reduce the number and severity of outbreaks. Three drugs are available for herpes treatment: acyclovir (Zovirax, GlaxoSmithKline, Research Triangle Park, NC), famciclovir (Famvir, Novartis Pharmaceuticals, East Hanover, NJ), and valacyclovir (Valtrex, GlaxoSmithKline).

According to the CDC, clinicians can choose from one of the following regimens for treatment of the first clinical episode of herpes:

- acyclovir 400 mg orally three times a day for seven to 10 days, or acyclovir 200 mg orally five times a day for seven to 10 days;
- famciclovir 250 mg orally three times a day for seven to 10 days;
- valacyclovir 1 g orally twice a day for seven to 10 days.

For episodic treatment of recurrent genital herpes, the CDC recommends clinicians choose one of the following approaches:

- acyclovir 400 mg orally three times a day for five days, or acyclovir 200 mg orally five times a day for five days, or acyclovir 800 mg orally twice a day for five days;
- famciclovir 125 mg orally twice a day for five days;
- valacyclovir 500 mg orally twice a day for three to five days, or valacyclovir 1 g orally once a day for five days.

For suppressive therapy of recurrent genital herpes, choose from one of the following treatment regimens, advises the CDC:

- acyclovir 400 mg orally twice a day;
- famciclovir 250 mg orally twice a day;
- valacyclovir 500 mg orally once a day, or valacyclovir 1 g orally once a day.[4]

## Reduce HSV transmission

Results of a randomized, double-blind, placebo-controlled trial of valacyclovir, which enrolled 1,494 monogamous, heterosexual couples in which one partner had serologically documented infection with HSV-2 and the other was HSV-2-seronegative, suggest that the drug reduces the likelihood of sexual transmission to the uninfected partner.[5]

Since suppressive therapy does not entirely prevent clinical recurrences of genital herpes or subclinical viral shedding, patients who use this drug regimen for HSV transmission also should be counseled on consistent use of condoms and abstinence during symptom flare-ups.

Researchers are beginning a new clinical study to examine the use of Famvir in daily treatment vs. treatment only at the time of outbreaks. This study may help providers optimize their management of genital herpes.

"Our goal as physicians is to help patients feel better and to reinforce the need to practice safer sex," states **Jennifer Berman**, MD, co-director of the Female Sexual Medicine Center at the University of California, Los Angeles. "For those already infected, the study will provide guidance on how better manage patients with genital herpes."

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