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Interpreting News and Research on Contraceptives and STIs

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IN THIS ISSUE

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The `Get It and Forget It' methods are here: Remove obstacles to use

St. Louis project promotes use of long-acting reversible contraception

Where do long-acting reversible contraceptives (LARC) fit in at your facility? How are you encouraging women to use the "Get It and Forget It" methods? If you are seeing low numbers of women choosing intrauterine devices (IUDs) or the contraceptive implant, you might want to change your counseling strategy.

Take a tip from the Contraceptive CHOICE Project in St. Louis. This project is a prospective cohort study of women ages 14-45 who want to avoid pregnancy for at least one year and are initiating a new form of reversible contraception.

Women screened for this study are read a script regarding long-acting reversible methods of contraception to increase awareness of these options. Participants choose their contraceptive method that is provided at no cost. From the beginning, the emphasis is placed on the effectiveness of the LARC methods compared to pills, the contraceptive patch, and the contraceptive vaginal ring.

The project enrolled 9,256 women. The first woman enrolled in August 2007, with the last woman entered in September 2011. Of those women enrolled in the program, 75% have chosen an IUD or an implant. Among women who chose these methods, 86% are still using them at one year. Just 55% of women who chose other methods, such as the Pill, ring, and contraceptive patch, maintained method use at the same point.

Women using the LARC methods and the contraceptive injection had the lowest unintended pregnancy rates at one, two, and three years of follow-up.

EXECUTIVE SUMMARY

The Contraceptive CHOICE Project in St. Louis has been successful at boosting use of long-acting reversible contraceptives (LARC).

- Of the first 5,086 women ages 14-45 enrolled in the project, 69% of women ages 14-17 and 61% of women ages 18-20 chose a LARC method. About 65% of women ages 14-17 chose the implant, while 71% of those ages 18-20 picked the IUD. All contraceptive methods have been provided at no cost to all women in the project.
- In the project design, researchers chose to present the most effective methods first in contraceptive counseling session.

Pill, ring, and patch users had much higher unintended pregnancy rates, more than 16 times higher than LARC users in Year One. *(Visit the project's website, www.choiceproject.wustl.edu, and click on "Study Findings" to obtain more statistics from the project.)*

Of the first 5,086 women ages 14-45 enrolled in the CHOICE Project, 69% of women ages 14-17 and 61% of women ages 18-20 chose a LARC method.

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

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Editorial Questions

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

About 65% of women ages 14-17 chose the implant, while 71% of those ages 18-20 picked the IUD.[1]

Despite a 2007 committee opinion from the American Congress of Obstetricians and Gynecologists recommending the T380A and levonorgestrel IUDs for adolescents, many clinicians remain reluctant to provide IUDs to young women.[2] Findings from a study of California providers indicated only 39% considered a teen to be an appropriate IUD candidate.[3] In a survey of St. Louis providers, just 31% of providers considered an IUD appropriate for teens, 50% would insert one for a 17-year-old with one child, and only 19% would insert one for a 17-year-old without any pregnancies.[4]

What are the most popular forms of contraception used by adolescents? According to the latest findings from the National Survey of Family growth, they are condoms and withdrawal, followed by birth control pills.[5] Just 3.6% of women ages 15-19 used the IUD, and the implant was not included as a separate method.[6] This use of less-reliable methods likely contributes to the 80% unintended pregnancy rate of adolescent women.[7]

The U.S. adolescent pregnancy rate rose for the first time in 2006, after a steady decline in the past 15 years. The rate increased by 3% over the 2005 rate in women ages 15-19.[8]

"This finding certainly suggests that all providers of contraceptives in the United States need to learn from and adopt approaches used by the St. Louis Contraceptive CHOICE Project to increase use of LARC methods," says **Robert Hatcher**, MD, MPH, professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta.

What drives LARC choice?

Why have so many women chosen LARC methods in the CHOICE Project?

For the answer, we look to **Jeffrey Peipert**, MD, MPH, MHA, Robert J. Perry professor of obstetrics and gynecology and vice chair for clinical research at Washington University School of Medicine in St. Louis, who is directing The Contraceptive CHOICE study. Peipert notes five factors:

- Women desire effective methods of contraception, and these methods are the most effective.
- All providers involved in the project believe in LARC methods and are willing to use them in almost all women.
- Access and affordability barriers are removed. All methods are provided free of charge and can be obtained easily at the project's health center.
- Providers dispel the myths and misconceptions

about these methods.

• Providers offer education and counseling regarding side effects and management of side effects.

For **Andrew Kaunitz**, MD, professor and associate chair in the Obstetrics and Gynecology Department at the University of Florida College of Medicine — Jacksonville, the Contraceptive CHOICE Project is reminiscent of the 1989 movie, "Field of Dreams." In that movie, Kevin Costner heard a voice that indicated "if you build it, he [Shoeless Joe Jackson] will come." Peipert and his group have convincingly demonstrated that if providers make long-acting reversible contraceptives available, women will make them their first-choice birth control option, says Kaunitz.

"Findings from the Contraceptive CHOICE Project represent the type of authoritative data that should result in changing our contraceptive paradigm," notes Kaunitz. "Given their high continuation and low failure rates, LARC methods should be first-line contraceptives for our patients; if, and only if, such methods are not suitable or accessible, then shorter-acting methods — pills, patches, rings — represent appropriate choices."

Check the order

When you talk with women regarding their birth control options, when do LARC methods enter the conversation?

During contraceptive counseling at the CHOICE Project, methods are presented in order of effectiveness, explains **Gina Secura**, PhD, adjunct assistant professor of epidemiology and senior scientist/epidemiologist in the Department of Obstetrics and Gynecology in the Division of Clinical Research at Washington University. According to Secura, the counselor presents the information about effectiveness, side effects, advantages, and disadvantages for each method in order of effectiveness. Counselors also advocate the dual use of condoms for prevention of sexually transmitted infections. Free condoms are available to all participants.

What is the order of presentation of methods at the CHOICE Project? The "top tier" reversible methods (intrauterine and implant contraceptives) lead the way:

• levonorgestrel intrauterine system (LNG-IUS, Mirena, Bayer HealthCare Pharmaceuticals, Wayne, NJ);

• copper T380A IUD (ParaGard, Teva Women's Health, North Wales, PA);

• contraceptive implant (Implanon, Merck & Co., Whitehouse Station, NJ);

• contraceptive injection (depot medroxyprogesterone acetate, DMPA; Depo-Provera, Pfizer, New York City; Teva Pharmaceuticals USA, North Wales, PA);

• oral contraceptives;

• contraceptive vaginal ring (NuvaRing, Merck & Co.);

• contraceptive patch (Evra, Ortho Women's Health & Urology, Raritan, NJ). *[An illustration of typical rates of contraceptive effectiveness, developed by the World Health Organization, can be found on p. 52 of the 20th revised edition of* Contraceptive Technology *(Ardent Media). The chart also may be viewed online at Planned Parenthood's website. Go to www.plannedparenthood.org. Under "The Facts On," select "Birth Control," then select "Compare Effectiveness of Birth Control Options."]*

How long to use IUDs?

The approved duration of use of the levonorgestrel IUD is five years, although studies have shown contraceptive efficacy to seven years.[9]

According to *A Clinical Guide For Contraception*, "the LNG IUD can be used for at least seven years, and probably 10 years."[10] The contraceptive implant is marketed with a duration of action for three years; however, pharmacokinetic data from Implanon users show stable serum concentrations of etonogestrel out to 36 months, suggesting that the method is effective for longer than that.[11] Three studies in which a total of 275 used Implanon for longer than three years found no pregnancies during the fourth year of use.[11]

Researchers at Washington University in St. Louis are conducting the Evaluation of Prolonged Use of IUD/Implanon for Contraception (EPIC) Study to confirm whether the levonorgestrel IUD and the subdermal implant are effective for longer than their current Food and Drug Administration-approved durations, reports Peipert. If these methods can be left in place for a longer period of time, they will be even more cost-effective, he notes.

"Imagine a 400-pound woman who comes in for IUD removal after five years of [Mirena] use; it may be very difficult to remove the Mirena and to reinsert," notes Peipert. "We can avoid the potential risks of this procedure if the device is actually effective for seven, 10, or 12 years."

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Circumcision devices eyed in HIV prevention

Now that male circumcision has been associated with a lower risk for HIV infection in international observational studies and in three randomized controlled clinical trials, international health officials are looking at options in making it more available to men at risk.[1-3]

Researchers are looking at two potential devices, the PrePex and the Shang Ring. Both of the devices are minimally invasive, with no need for hemostasis or suturing, making the procedures quicker and easier to perform, even by non-surgeons, and potentially safer and more acceptable to patients. Data from studies of these devices recently were presented at the 16th International Conference on AIDS and STIs in Africa in Addis Ababa, Ethiopia.[4,5] *(Why are such devices needed? See the information on p. 41.)*

Rings minimize bleeding

The Shang Ring, manufactured by Wu Hu SNNDA Medical Treatment Appliance Technology Co., Wu Hu City, China, is a disposable circumcision device consisting of two concentric plastic rings. The foreskin is everted over the inner ring before application of the outer ring, and then the foreskin is cut off from the underside using scissors. Hemostasis provided by compression of the foreskin between the locking rings prevents bleeding and averts the need for sutures.

The Shang Ring is similar to the Plastibell device that is widely used in the United States for infant male circumcision in that it remains on the penis after the procedure. While the Plastibell device falls off after several days, the Shang Ring stays on longer, because adults heal more slowly than infants. Labeling for the device recommends removal of the Shang Ring on the seventh day after it is administered.[6]

A randomized controlled trial was conducted at Nyanza, Kenya's Homa Bay District Hospital and the Society for Family Health's New Start YWCA Male Circumcision Centre in Lusaka, Zambia. The trial was conducted to compare the use of the device with conventional surgery. At each site, 198 men seeking male circumcision randomly were assigned to be circumcised by surgeons using the Shang Ring or the conventional technique. Preliminary results of the trial show that rates of complications from the surgery were low and similar in both groups. All complications experienced with the Shang Ring were mild or moderate and were resolved with conservative management, researchers note.[4] Use of the Shang Ring reduced the average time it took to perform the procedure from 20 minutes to 7 minutes in Kenya and to 6.5 minutes in Zambia. All of the procedures in Zambia and about half of the procedures in Kenya were performed by nurses or clinical officers rather than physicians.[4]

The Bill & Melinda Gates Foundation is funding research evaluating the Shang Ring, confirms **Julie Bernstein**, a senior communications officer with the organization. The foundation also supports the World Health Organization's efforts to evaluate and provide guidance on the safety and efficacy of male circumcision devices, she notes.

EXECUTIVE SUMMARY

International health officials are looking at options for adult male circumcision now that it has been associated with a lower risk for HIV infection in international observational studies and three randomized controlled clinical trials.
• Researchers are looking at two potential devices, the PrePex and the Shang Ring. With both of the devices, no stitches are required, which makes the procedure easier to perform, even by non-surgeons, and potentially safer and more acceptable to patients.
• Findings from an analysis of 14 priority countries in eastern and southern Africa indicate that by increasing male circumcision services to cover 80% of all adult men and newborn boys between 2009 and 2015, more than 4 million new adult HIV infections could be averted, at a cost savings of $2.5 billion.

FHI 360, a Research Triangle Park, NC-based human development organization, and its collaborators are thankful for the Gates Foundation's support and are encouraged by the results of their Shang Ring research, says **David Sokal**, MD, FHI 360 scientist and principal investigator for the Shang Ring grant. "Men prefer the improved cosmetic results compared to the results after suturing, and providers have told us it's much easier than conventional surgery," Sokal comments.

PrePex eyed in trials

The PrePex device, developed by Circ MedTech of the British Virgin Islands, uses a special elastic mechanism that fits closely around an inner ring to trap the foreskin in between. No anesthesia, sutures, or sterile settings are required, say its developers. Once the foreskin necrotizes, the device is safely removed in a week, and the necrotic foreskin is cut off.

To assess the safety and effectiveness of male circumcision using the PrePex device, researchers recruited 10 Rwandan nurses who had no prior experience performing male circumcisions. The nurses were trained for three days and then used the device to circumcise 590 men in a procedure that required no injected anesthesia.

All of the procedures were performed successfully, with two resulting in device-related complications. No serious complications were reported, and all were resolved easily, researchers report. The device has the potential to facilitate rapid, safe scale-up of male circumcision performed by healthcare providers who are not physicians, researchers conclude.[5]

It is "remarkable" how quickly those who have been trained in device use can perform procedures with minimal adverse effects, says **Steven Kaplan**, MD, a urologist at Weill Cornell Medical College. Kaplan, who is serving as a co-investigator in PrePex research, says he believes the procedure can be done by healthcare extenders with very good success.

While the PrePex device has received 510k marketing clearance in the United States by the Food and Drug Administration, there are no current plans to bring it to the U.S. market.

"The company has no plans for the U.S. market," says **John Keaten**, a spokesperson for the Acumen Fund in New York City, a nonprofit venture firm that has invested in Circ MedTech. "It is strictly focused on voluntary adult male circumcision for HIV prevention in resource-limited settings."

The World Health Organization has established an independent advisory committee to systematically review data from circumcision studies. Research of the Shang Ring and the PrePex devices are part of a series of assessments designed to establish the safety, effectiveness, and acceptability of adult male circumcision devices in different settings before public health officials proceed with more widespread implementation in sub-Saharan Africa.[7]

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What is the reason devices are needed?

While circumcision might not be a "silver bullet" in addressing the international AIDS epidemic, public health officials consider it a critical component in the HIV prevention "toolkit," particularly in such hard-hit regions as sub-Saharan Africa.[1] Findings from an analysis of 14 priority countries in eastern and southern Africa indicate that by increasing male circumcision services to cover 80% of all adult men and newborn boys between 2009 and 2015, more than 4 million new adult HIV infections could be averted at a cost of $2.5 billion.[2]

A dilemma lies in the shortage of providers trained to perform a classical circumcision. Even if men can be gathered to perform circumcisions, each procedure takes about 15 to 20 minutes in the hands of a skilled surgeon, and most African countries are desperately short of such healthcare professionals.[3]

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Pfizer issues recalls for Akrimax OCs

Has your clinic telephone been ringing recently with calls from women who have heard about a birth control pill recall? Chances are, few, if any, of your patients were using the affected oral contraceptives (OCs).

The voluntary recall was announced Jan. 31, 2012 by the manufacturer of the drug, Pfizer of New York City. The recall involves 14 lots of Lo/Ovral-28 (norgestrel and ethinyl estradiol) tablets and 14 lots of norgestrel and ethinyl estradiol tablets (generic) contraceptives labeled under the Akrimax Pharmaceuticals brand. The product is distributed to warehouses, clinics, and retail pharmacies nationwide. *(See the table, p. 43, for the affected lots.)*

While the recall includes around one million pill packets, it is likely few of your patients were using them. The two pills are not often prescribed; according to 2010 sales data from IMS Health, they represent less than 2% of the OC market.[1] *[Did you receive the* Contraceptive Technology Update *bulletin on the recall? To receive future bulletins, provide your e-mail address to AHC Media customer service at (800) 688-2421 or customerservice@ahcmedia.com.]*

EXECUTIVE SUMMARY

Pfizer announced a voluntary recall Jan. 31, 2012, of 14 lots of Lo/Ovral-28 (norgestrel and ethinyl estradiol) tablets and 14 lots of norgestrel and ethinyl estradiol tablets (generic) contraceptives labeled under the Akrimax Pharmaceuticals brand.

- While the recall includes around one million pill packets, it is likely few patients were using them. The two pills are not often prescribed. According to 2010 sales data from IMS Health, they represent less than 2% of the oral contraceptive market.
- Some blister packs of the drug might contain an inexact count of inert or active ingredient tablets, and the tablets might be out of sequence, according to the company. The packaging error has since been rectified

What happened?

According to a Pfizer press release, a company investigation found that some blister packs of the drug might contain an inexact count of inert or active ingredient tablets and that the tablets might be out of sequence. The company says the cause of the packaging error has since been rectified. The pills were packaged at a manufacturing plant in Rouse's Point, NY.[1]

"As a result of this packaging error, the daily regimen for these oral contraceptives may be incorrect and could leave women without adequate contraception and at risk for unintended pregnancy," the company press release states. "These packaging defects do not pose any immediate health risks; however, consumers exposed to affected packaging should begin using a non-hormonal form of contraception immediately."

The company also advises patients who have affected product to notify their healthcare provider and return the product to the pharmacy. [Any adverse events that might be related to the use of the affected product should be reported to Akrimax Medical Information by telephoning (877) 509-3935, 8 a.m. to 7 p.m. Monday-Friday, Central Time. Adverse events also may be reported to the Food and Drug Administration's MedWatch Program. Go to www.fda.gov/Safety/MedWatch/default.htm, and click on "Report A Serious Medical Product Problem Online" to access Form FDA 3500. Events may be entered online, or the form may be printed and mailed to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787 or faxed to (800) 332-0178.]

Recalls aren't new

Family planners are familiar with product recalls. Qualitest of Huntsville, AL, pulled multiple lots of oral contraceptives Sept. 15, 2011, after the manufacturer detected a packaging error that could lead to incorrect administration of several brands of its pills. In 2003, Barr Laboratories of Pomona, NY, issued a recall of certain lots of its Nortrel 7/7/7 OC after the company received two reports that color-coded tablets in the drug's blister card were not in correct order. (*To review the recalls, see the* Contraceptive Technology Update *articles "Qualitest pulls suspect OCs, December 2011, p.*

Affected Lots of Recalled Akrimax OCs

NDC	Product	Lot	Expiration	Configuration/Count
24090-801-84	LO/OVRAL® 28	E15678	08/31/2013	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15679	08/31/2013	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15686	08/31/2013	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15687	01/31/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15690	01/31/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15698	01/31/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E15700	02/28/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E80434	07/31/2013	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	E80438	08/31/2013	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	F36908	02/28/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	F36909	02/28/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	F43915	03/31/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	F43926	03/31/2014	6 Pilpacks® of 28 tablets each
24090-801-84	LO/OVRAL® 28	F43927	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	E15677	08/31/2013	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	E15704	01/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	E15706	01/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	E80440	08/31/2013	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F16388	01/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F16390	02/28/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F22132	02/28/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F31330	02/28/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F36911	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F36913	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F43924	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F43925	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F43934	03/31/2014	6 Pilpacks® of 28 tablets each
24090-961-84	Norgestrel 0.3 mg/Ethinyl Estradiol 0.03 mg	F53238	03/31/2014	6 Pilpacks® of 28 tablets each

137, and "Check Nortrel stock — Barr Labs issues recall," September 2003, p. 100.)

Other contraceptive recalls include the 2000 alert regarding the Norplant contraceptive implant and the 2002 recall on the Lunelle contraceptive injection. Neither of those products is on today's market.

What should you do in the event of such a recall? Offer women emergency contraception, advocates Susan Wysocki, WHNP-BC, FAANP, president & chief executive officer of iWomen's Health in Washington, DC. EC is available in the form of the behind-the-counter emergency contraceptive pills Plan B (Teva Pharmaceuticals, Woodcliff Lake, NJ) and Next Choice (Watson Pharmaceuticals, Parsippany, NJ); prescription-only Ella (HRA Pharma, Paris, France); or the Copper T 380A intrauterine device (ParaGard, Teva Pharmaceuticals).

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Ulipristal acetate: New fibroid treatment?

Ulipristal acetate, the drug recently approved as an emergency contraceptive in the United States (Ella, Watson Pharmaceuticals, Morristown, NJ), is being eyed for other gynecologic uses. In research looking at women with symptomatic fibroids who were planning to undergo surgery, treatment with the selective progesterone-receptor modulator was effective in controlling excessive bleeding and reducing fibroid size at 13 weeks.[1,2]

Fibroids, also known as uterine leiomyomas, are the most common benign uterine tumors in women of reproductive age.[3] In addition to anemia caused by heavy bleeding, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility. While most fibroids are treated with surgical or radiologic interventions, options for medical therapy are limited.

Which women might best benefit from medication management of uterine fibroids? Two groups come to mind, says lead investigator of the two trials,

EXECUTIVE SUMMARY

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- Fibroids are the most common benign uterine tumors in women of reproductive age. In addition to anemia caused by heavy bleeding, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility.
- While most fibroids are treated with surgical or radiologic interventions, options for medical therapy are limited. Leuprolide is considered the most effective medical therapy available for fibroid treatment.

Jacques Donnez, MD, PhD, professor at the Cliniques Universitaires Saint-Luc Catholic University of Louvain in Brussels, Belgium. They are:

- all women suffering from menorrhagia due to the presence of myomas;
- the large group of women (ages 40-50) with large myomas.

The goal is to avoid hysterectomy, says Donnez. Fibroids remain the leading cause of the surgical procedure.[4]

Take a closer look

The recently published research includes two investigations.

One of the investigations is a placebo-controlled dose-ranging trial.[1] The other is a noninferiority trial comparing the same two doses of ulipristal acetate with injections of leuprolide, a gonadotropin-releasing hormone (GnRH). Leuprolide is considered the most effective medical therapy available for fibroid treatment.[5]

Both studies included premenopausal women, ages 18-50, with symptomatic fibroids, including heavy menstrual bleeding who were eligible for hysterectomy. In addition to heavy menstrual bleeding, patients in the dose-finding trial had to be anemic; all women in the investigation received concomitant oral administration of iron.

In the dose-finding trial, both 5 mg and 10 mg daily doses were highly effective in reducing menstrual blood loss. Researchers report about 75% of women treated with ulipristal acetate became amenorrheic.[1]

In the trial looking at ulipristal acetate and leuprolide, control of excessive bleeding was more rapid in patients receiving ulipristal acetate than in those receiving leuprolide. Median times to amenorrhea were seven days for patients receiving 5 mg ulipristal acetate, compared to five days for those receiving 10 mg of the drug and 21 days for those receiving leuprolide.

In the investigation looking at ulipristal acetate and leuprolide, women could elect to have surgery following their 13-week treatment course. All treatments reduced the volume of the three largest fibroids; median reductions were seen at week 13 in 36% of the 5 mg ulipristal acetate group, compared to 42% of the 10 mg ulipristal acetate group and 53% of the group receiving leuprolide. For those patients who did not undergo hysterectomy or myomectomy, researchers noted that ulipristal acetate had a more sustained effect on the reduction of fibroids volume during the six months follow up without further treatment than did leuprolide acetate.[2]

Investigators noted no major safety concerns with ulipristal acetate during the 13-week trial; it had little impact on serum estrogen levels and bone markers, and it did not cause hot flashes. While nonphysiologic endometrial changes associated with progesterone-receptor modulators occurred in almost two-thirds of women receiving ulipristal acetate during their treatment, such changes resolved six months following discontinuation of the study drug.[2]

The profound hypoestrogenism associated with GnRH agonist administration represents a major disadvantage in treating symptomatic fibroids, notes **Andrew Kaunitz,** MD, professor and associate chair in the Obstetrics and Gynecology Department at the University of Florida College of Medicine — Jacksonville. "Although the endometrial changes associated with current use of ulipristal acetate appear to be benign, the endometrial safety of this class of medications will not be resolved until longer-term studies are conducted," Kaunitz notes.

What's the next step?

PregLem, a Swiss-based specialty biopharmaceutical subsidiary of Hungarian-based pharmaceutical manufacturer Gedeon Richter, recently has received positive feedback from the European Medicines Agency in seeking European marketing authorization of the drug. Trademarked as Esmya, it will be used in pre-operative treatment of uterine fibroids.

There remains a substantial need for effective medical therapy of fibroids, according to an editorial accompanying the two published studies.[6] Findings of the two trials point not only to a role for ulipristal acetate in preoperative treatment but, with more study, a possible effective long-term or intermittent medical approach to treating selected patients with symptomatic fibroids, says Kaunitz.

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HPV shot doesn't trigger autoimmune response

New research indicates that the human papillomavirus vaccine (HPV) Gardasil (Merck & Co.) does not trigger autoimmune conditions such as lupus, rheumatoid arthritis, type 1 diabetes, or multiple sclerosis after vaccination in young women.[1] Such news might be reassuring to parents who have withheld the vaccine from their children due to perceived safety concerns surrounding immunization.

To conduct the study, researchers at Kaiser Permanente in Pasadena used electronic health records from 189,629 females ages 9-26 in California who were followed for six months after receiving each dose of the quadrivalent HPV vaccine in 2006-2008. The data indicated no increase in 16 pre-specified autoimmune conditions in the vaccinated population compared to a matched group of unvaccinated girls and women.[1]

What are the most important strengths of the study? There are two, says lead author **Chun Chao**, PhD, a research scientist at the Department of Research & Evaluation at Kaiser Permanente Southern California, and adjunct assistant professor in the Department of Epidemiology at University of California, Los Angeles. The first lies in the in-depth chart review by physician experts for diagnosis confirmation and to determine the timing of disease onset, so as to ensure disease onset was after vaccination.

The second strength comes from the statistical approach in comparing the incidence of autoimmune conditions among females vaccinated versus females in the same age range but who were not vaccinated, she says.

"Other strengths include casting a wide net initially to capture all potential new onset autoimmune cases, adequate follow-up time for capturing onset of autoimmune disease, which usually requires some clinical work-up before the diagnosis is made, and a large, diverse, yet well-defined study population," Chao states.

Checking shot safety

Autoimmune reactions have been a longstanding concern surrounding vaccination of all types. Many parents withhold vaccine from their children because of perceived safety concerns.[2] However, most associations have stemmed from case reports that have not been confirmed by large, controlled epidemiologic studies.[3]

The current study looked for autoimmune conditions such as immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes, Hashimoto's disease, Graves' disease, multiple sclerosis, acute disseminated encephalomyelitis, other demyelinating diseases of the central nervous system, vaccine-associated demyelination, Guillain-Barré syndrome, neuromyelitis optica, optic neuritis, and uveitis.

To perform the analysis, the researchers identified potential new-onset cases through review of electronic medical records of 149,306 women who had been members of Kaiser Permanente health plans for at least 12 months. Cases identified between January 2004 and the first vaccine were classified as pre-existing and were excluded. The researchers then used the incidence of each condition among vaccinated women and compared it with an estimated incidence for unvaccinated women, which was derived using multiple imputations. Each finding was expressed as an incidence rate ratio (IRR).

Of 719 cases eligible for review, from 31% to 40% of the conditions found were confirmed as new-onset. No IRR was significantly elevated except that for Hashimoto's disease (IRR, 1.29; 95% confidence interval,1.08 - 1.56); however, the investigators concluded there was no consistent evidence for a safety signal for autoimmune thyroid conditions.

EXECUTIVE SUMMARY

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Males now included

The recent publication of 2012 immunization schedules by the Advisory Committee on Immunization Practices (ACIP) confirms the panel's 2011 recommendation that males be routinely vaccinated against HPV.[4] The ACIP recommended routine vaccination of males ages 11 or 12 with three doses of the quadrivalent HPV vaccine. The recommendation includes that vaccination can begin as young as age 9, and that boys and young men ages 13 to 21 who have not already received the vaccine also should be immunized. The second dose should be administered one to two months after the first dose, and the third dose should be administered six months after the first dose. *(*Contraceptive Technology Update *covered the committee's recommendation; see "Finally! HPV male shot routinely recommended," January 2012, p. 6.)* The American Academy of Pediatrics also has included routine vaccination for males in its 2012 immunization schedule.[5]

"The elimination of this virus would be beneficial to everyone," says **Garry Sigman**, MD, adolescent medicine expert at Loyola University Health System in Chicago. "This is a vaccine that has been proven to be effective in eliminating a deadly virus. It should be treated like every other vaccine."

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COMING IN FUTURE MONTHS

- Emerging threat: untreatable gonococcal infections
- Teen pregnancies down, but disparities remain
- Tenofovir linked to risk of kidney damage
- Check use of lubricant in speculum exams

Study confirms impact of OCs on dysmenorrhea

Results from a large, long-running Scandinavian study provides convincing evidence that combined oral contraceptives (OCs) alleviate the symptoms of dysmenorrhea, painful menstrual periods.[1]

Although results of earlier studies have suggested that combined OCs could have an impact on painful periods, a 2009 review of available research concluded there was limited evidence for pain improvement with use of the Pill in women with dysmenorrhea.[2]

Having definitive evidence helps clinicians move forward in addressing this common concern. Dysmenorrhea occurs frequently, particularly in young women; in some studies, up to 91% of female adolescents report painful periods.[3,4]

The current research stems from a Scandinavian study that has been running for 30 years.[5] To perform the 2012 study, researchers from the University of Gothenburg questioned three groups of women who reached age 19 in 1981, 1991, and 2001. Each group included some 400 to 520 women, who provided information on height, weight, reproductive history, pattern of menstruation and menstrual pain, and contraceptive use. The women were assessed again at age 24.

Each woman was her own control

By comparing the same women at two ages, the scientists were able to use each woman as her own control, which allowed them to establish whether any reduction in severity of symptoms was due to Pill use or increasing age. Current severity of dysmenorrhea was measured on each occasion by a verbal multidimensional scoring system and by a visual analogue scale.

In the 2009 review of all available data, reviewers noted earlier data from the original Swedish study indicating a lower prevalence and severity of dysmenorrhea in women who were Pill users.[5] The 2009 review concluded the efficacy of combined pills against dysmenorrhea could be attributed to the passage of time, notes **Ingela Lindh**, SRN, SRM, a researcher at the Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg. To test that conclusion, the 2012 research team analyzed data taking into account the influence of time as a confounding factor, states Lindh, lead author of the current paper. Its conclusion? Combined oral contraceptives, independent of age, influence the prevalence and severity of dysmenorrhea, states Lindh.

EXECUTIVE SUMMARY

Results from a large, long-running Scandinavian study provides convincing evidence that combined oral contraceptives (OCs) alleviate the symptoms of dysmenorrhea.

• Although results of earlier studies have suggested that combined OCs could have an impact on painful periods, a 2009 review of available research concluded there was limited evidence for pain improvement with use of the Pill in women with dysmenorrhea.

• Dysmenorrhea occurs frequently, particularly in young women. In some studies, up to 91% of female adolescents report painful periods.

In a 2011 analysis of data from the 2006–2008 National Survey of Family Growth, 31% of all pill users ages 15-44 said they used OCs for cramps or menstrual pain.[6] In the case of teens, 54% said they chose OCs primarily for menstrual pain.

Current low-dose (20 mcg) oral contraceptives are an effective treatment choice for moderate to severe dysmenorrhea in adolescents, according to a 2005 study.[7] The paper was one of the first looks at current pills; earlier studies focused on higher-dose formulations. *(To read more about the study, see the* Contraceptive Technology Update *article, "Teens & dysmenorrhea: look to low-dose OCs," September 2005, p. 108.)*

For women with heavy periods, pain is the most commonly reported problem.[8] The more severe a woman's pain is, the more effective combined oral contraceptives are in reducing her symptoms; research indicates a reduction of almost 90% in severe dysmenorrhea.[9]

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) might be a first-line choice for women with painful periods who don't wish to use a contraceptive method.[10] However, for women who wish pregnancy prevention, combined OCs are the preferential therapy for pain relief from dysmenorrhea. Pills confer the additional noncontraceptive benefit of pain relief from dysmenorrhea, are not linked to additional risks, eliminate the risks associated with taking NSAIDs, and are a more suitable long-term option for women with dysmenorrhea.[10]

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CNE/CME QUESTIONS

1. What are the "top-tier" reversible contraceptive methods?
   A. Intrauterine contraceptives and the contraceptive implant
   B. Intrauterine contraceptives, the contraceptive implant, and the contraceptive injection
   C. Intrauterine contraceptives, the contraceptive implant, and the contraceptive vaginal ring
   D. Combined oral contraceptives, the contraceptive vaginal ring, and the contraceptive patch.

2. What are the two devices being evaluated for potential use in adult male circumcision?
   A. PrePex and Shang Ring
   B. IntraVas and BioRing
   C. RISUG and BioRing
   D. ProVas and Shang Ring

3. What are the brand of pills involved in the January 2012 contraceptive recall?
   A. Ortho Tri-Cyclen
   B. Akrimax Pharmaceuticals Lo/Ovral-28 and norgestrel and ethinyl estradiol tablets
   C. Ortho Novum
   D. Alesse

4. What drug is now being eyed as a potential treatment for symptomatic fibroids?
   A. Cytotoxic gold compounds
   B. Isosorbide mononitrate
   C. Chitosan
   D. Ulipristal acetate

CNE/CME OBJECTIVES & INSTRUCTIONS

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.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

Contraceptive Technology Update is endorsed by the National Association of Nurse Practitioners in Women's Health and the Association of Reproductive Health Professionals as a vital information source for healthcare professionals.