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INSIDE

RELIAS MEDIA

Expanding Intrauterine Contraceptive Choices: Science Seeks Options

Smaller copper devices in advanced research studies

Today, 4.4 million women in the United States rely on an intrauterine device (IUD) for contraception.[1] According to a 2018 analysis, this level of IUD use represents the greatest percentage of device use ever seen in the U.S. Almost 8% of all women, nearly 12% among women using contraception, and more than 16% of reversible contraception users named the IUD in a national survey.[2] This uptick stands in sharp contrast to the less than 1% of women who used the device in 1995.

The copper T 380A was one of the few IUDs available for Americans in 1995. Introduced in the U.S. in 1988, it is an extremely effective form of birth control, with a failure rate of 0.3%-0.6%.[3] The device features a 380 mm^2 copper surface area supplied by a sleeve of solid copper on each of the arms, with copper wire wrapped around the 36 mm vertical stem. A monofilament polyethylene thread is tied through the base, creating two 10.5 cm tailstrings for device detection and removal. The device is designed to be used in women whose uterine cavities sound to a depth of 6-9 cm.[3]

> "SOME PREVIOUS RESEARCH HAS SHOWN THAT SMALLER IUDS MAY FIT THE UTERI OF NULLIPAROUS WOMEN BETTER THAN THE STANDARD DEVICE."

The copper T 380A was designed nearly 50 years ago, notes **David Hubacher**, PhD, senior epidemiologist,

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product development and introduction at FHI 360 in Durham, NC.

"Over the past four decades, this product has become the predominant device that international donor agencies purchase for developing countries," states Hubacher. "The product has become the standard-bearer for copper devices due to its high effectiveness."

Research Underway on Copper Option

In collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development, FHI 360 is leading a clinical trial comparing the standard copper T 380A with a newer, smaller copper IUD not sold in the United States. The study device measures 24 mm horizontally and 30 mm vertically, compared to the copper T 380A, which measures 32 mm horizontally and 36 mm vertically. The study's primary outcome measure is to determine the pregnancy rate over three years.

The device, the Mona Lisa NT Cu380 Mini, has been marketed in Europe since 2014 and is currently available in Canada, Germany, France, and eight other countries. It is labeled for use up to five years.[2]

All contraceptive products produce side effects. The goal of this comparative study is to see if a smaller copper IUD shows similar efficacy to the copper T 380A with fewer side effects, notes Hubacher.

"Side effects of increased menstrual bleeding and pain are the main reasons why women stop using the copper T 380A. Nulliparous women tend to have higher removal rates compared to parous women," says Hubacher. "Indeed, some previous research has shown that smaller IUDs may fit the uteri of nulliparous women better than the standard device."

In its original U.S. clinical trials, the two-year cumulative discontinuation rate for the copper T 380A was 22%; by three years, the rate rose to 33%, and after five years, discontinuation was at 60%.[4] In the CHOICE Project study, data indicated that at 24 months, 48 months, and 60 months, 23%, 35.8%, and 44.1%, respectively, of copper IUD users discontinued.[5] In a 2019 case control review, 67 women were fitted with a mini IUD (mean age 23 years, 64%

EXECUTIVE SUMMARY

The copper T 380A intrauterine device (IUD), developed almost 50 years ago, was introduced in the United States in 1988. It is an extremely effective form of birth control, with a failure rate of 0.3%-0.6%. It measures 32 mm horizontally and 36 mm vertically.

- Researchers are conducting a clinical trial comparing the device with a newer, smaller copper IUD not sold in the United States. The device, the Mona Lisa NT Cu380 Mini, has been marketed in Europe since 2014 and is available in Canada, Germany, France, and eight other countries. It carries a labeled duration of use of up to five years. It measures 24 mm horizontally and 30 mm vertically.
- A Phase III trial of the VeraCept IUD, a novel copper IUD on a flexible frame, is underway. The VeraCept measures 32 mm horizontally and 30 mm vertically.

nulliparous) and 63 women were fitted with a standard IUD (mean age 25 years, 39% nulliparous). Data indicated that more women who used the standard-sized IUD complained of pain and bleeding, leading to higher discontinuation at one year.[6]

"This trial of predominately nulliparous women is the first comparative study involving a smaller copper IUD to be conducted in the U.S. in more than 35 years," says Hubacher. "If participants experience fewer side effects and higher satisfaction with the smaller product, while simultaneously benefitting from high contraceptive efficacy, then this product will provide additional options for women seeking nonhormonal, long-acting contraception."

More Devices in Research Pipeline

The Phase III trial of the VeraCept IUD, a novel copper IUD on a flexible frame, is underway. The IUD's design accommodates the shape of the uterus with a lower total copper load for increased comfort and less bleeding. The flexible frame is made of nitinol, a nickel and titanium alloy.

During insertion, the 30 mm x 32 mm device is placed just inside the internal cervical os and bilaterally at the tubal ostia. For comparison, the copper T380 A measures 32 mm horizontally and 36 mm vertically.[7] The VeraCept features 175 mm^2 of copper surface area, which is less than the 380 mm^2 in the copper T 380A.

The VeraCept underwent a Phase II trial of 286 women in 12 U.S. centers who provided 4,263 cycles evaluable for pregnancy. Sixty percent of women enrolled in the study were nulliparous. One pregnancy occurred during the 24 months of observation (Pearl Index 0.30; 95% confidence interval, 0.01-1.70). Placement was successful in 283 women, with a mean pain score at insertion reported at 1.44. At one year, 177 women elected to continue device use, with 135 (76.2%) continuing to use the IUD until 24 months. About 15% of women discontinued early due to adverse events.[8]

In a randomized, subject-blinded comparison of the VeraCept IUD and a copper T 380A, data indicate use of the VeraCept device resulted in less pain at insertion, fewer expulsions, and higher total continuation than the copper T 380A, with similar efficacy.[9]

The Phase III trial is designed as a prospective, multicenter, single-arm, open-label study for three years, with extension up to five years. Women who are postmenarcheal and premenopausal up to age 45, who are at risk for pregnancy, and who desire a long-term intrauterine contraceptive for birth control are eligible for the study. Estimated completion date is 2024.

Sebela Pharmaceuticals also has a 52 mg levonorgestrel (LNG)-releasing system, the LevoCept, under development. The device has a nitinol wire frame with a 32 mm arm span and a 30 mm vertical measurement. There are two similar 52 mg levonorgestrel IUDs currently available in the United States: Mirena and Liletta. The FDA recently approved Liletta for up to six years of effective use; the manufacturers of the Mirena have requested approval for a similar effectiveness window. Cumulative pregnancy rates for the available 52 mg IUDs are 0.1% to 0.2% in the first year.[10] ■

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Drug Studied for Treatment of Fibroid-Associated Bleeding

Elagolix, a gonadotropin-releasing hormone (GnRH) antagonist currently used in the treatment of endometriosis pain, is now being studied for treatment of uterine fibroids and heavy menstrual bleeding in women.[1] The drug, marketed as Orilissa, was approved by the FDA in July 2018 for the treatment of moderate to severe endometriosis pain.

Researchers enrolled 790 women, ages 18-51 years who experienced heavy bleeding due to fibroids, into two identical, double-blind, randomized, placebo-controlled, six-month Phase III trials. Participants were randomly assigned to three study arms. The first group received elagolix, which reduces the production of estrogen and progesterone. Scientists believed it would shrink fibroid size and reduce bleeding. The second group received elagolix and a low dose of estrogen and progestin, with the aim of reducing hot flashes and bone loss, two side effects of elagolix. The remaining group received identical placebo pills. All study participants underwent ultrasound to confirm uterine fibroids and heavy menstrual bleeding (defined as more than 80 mL of blood loss per cycle) for at least two cycles. One trial was conducted at 76 sites in the United States from December 2015 through December 2018. The second trial was performed at 77 sites in the U.S. and Canada from February 2016 through January 2019.

Check Treatment Options

Researchers reported that 80.4% of the women treated with elagolix alone experienced a 50% or more reduction in menstrual bleeding, compared to 9.6% of the women in the placebo group. Seventy-two percent of women treated with elagolix and supplemental estrogen/progestin therapy reported a reduction of 50% or more. While women who were treated with elagolix alone showed more bone mineral loss compared with the women treated with placebo, there was no difference between the loss of bone mineral in the group treated with elagolix and the supplemental hormones as compared to those in the placebo group.[1]

Uterine fibroids account for one-third to one-half of all hysterectomies. Fibroids are associated with substantial morbidity and healthcare costs for reproductive-age women.[2]

Which nonsurgical treatment options are available for heavy menstrual bleeding due to fibroids? Uterine artery embolization and high-intensity focused ultrasound are two options, notes **William Schlaff**, MD, chair of the department of obstetrics and gynecology at the Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia. Schlaff led the two current trials of elagolix. Pharmaceutical approaches include GnRH analogs such as leuprolide acetate, as well as nonspecific hormonal treatments such as birth control pills. Medications and procedures may or may not be FDA-approved for use in treating fibroids, states Schlaff.

Tranexamic acid has been used as first-line treatment for heavy menstrual bleeding, and is frequently used for women with small fibroids despite limited evidence.[3] Use of mefenamic acid, a nonsteroidal anti-inflammatory drug commonly used for dysmenorrhea, has registered modest reduction in heavy menstrual bleeding in women without fibroids, although it is less effective than tranexamic acid.[3] No clinical trials have been conducted on its effect on fibroids.[4]

Ulipristal, a selective progesterone receptor modulator, is approved and marketed in Europe as Esmya for the preoperative and intermittent treatment of moderate to severe symptoms

EXECUTIVE SUMMARY

Elagolix, a gonadotropin-releasing hormone (GnRH) antagonist used to treat endometriosis pain, is being studied for treatment of uterine fibroids and heavy menstrual bleeding in women.

- The drug, marketed as Orilissa, was approved by the FDA in July 2018 for the treatment of moderate to severe endometriosis pain.
- Uterine fibroids account for one-third to half of all hysterectomies. They also are associated with substantial morbidity and healthcare costs for reproductive-age women. Pharmaceutical treatment approaches to heavy menstrual bleeding due to fibroids include GnRH analogs such as leuprolide acetate, as well as nonspecific hormonal treatments such as birth control pills.

of uterine fibroids in adult women of reproductive age. However, the FDA rejected approval of the drug in 2018 for such use in the United States because of concerns of liver injury. The European Medicines Agency issued new measures to protect women, including liver tests before, during, and after stopping treatment.[5]

Scientists also are examining relugolix, an oral GnRH antagonist, for use in fibroid treatment. In women with uterine leiomyomas, once-daily treatment with the drug demonstrated noninferiority to monthly leuprorelin in decreasing heavy menstrual bleeding.[6] The drug, under development by Myovant Sciences, is involved in two international advanced clinical trials. ■

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Generic Pre-Exposure Prophylaxis Set to Debut

Pre-exposure prophylaxis (PrEP), which consists of the anti-HIV drugs emtricitabine and tenofovir disoproxil fumarate (TDF/FTC, brand name Truvada), is recommended as a first-line resource for HIV prevention. However, the cost of Truvada, which averages around $24,000 per year in the United States, has been a major barrier to PrEP use. Estimates indicate that only about 270,000 people in the United States currently use PrEP.[1] With the drug set to debut as a generic in 2020, what will be the ramifications for PrEP use?

The introduction of generic TDF/FTC could expand access to PrEP in the U.S., says **Douglas Krakower**, MD, assistant professor at the Harvard Pilgrim Health Care Institute, Beth Israel Deaconess Medical Center, and Harvard Medical School.

"Some people who are likely to benefit from PrEP use may be hesitant or unable to do so because of out-of-pocket costs, such as high deductibles and copays," notes Krakower. "If the price of PrEP decreases substantially, which is most likely to occur once there are multiple generics available for prescribing, then it could be more affordable for larger numbers of people."

Generics could provide a more cost-effective option for PrEP, which could accrue savings from a societal perspective, states Krakower. Such savings would ideally provide an opportunity to reallocate funds toward supporting the nonmedication costs of PrEP care, such as provider fees and clinical monitoring, which also could improve PrEP uptake and effects, he notes.

"Economically disadvantaged communities experience disproportionately high numbers of new HIV infections, and also have the greatest challenges in accessing PrEP. The cost savings from generic TDF/FTC could hopefully be used to address this inequity," states Krakower.

EXECUTIVE SUMMARY

Pre-exposure prophylaxis (PrEP), which consists of the anti-HIV drugs emtricitabine and tenofovir disoproxil fumarate (TDF/FTC, brand name Truvada), is recommended as a first-line resource in HIV prevention. A generic version of the drug combination is set to be released in 2020.

- In October 2019, the FDA approved a second drug combination, tenofovir alafenamide with emtricitabine (Descovy), for PrEP in men who have sex with men, and transgender women.
- At a list price of around $24,000 a year, the cost of branded emtricitabine and tenofovir disoproxil fumarate has created barriers to PrEP access at all levels of the U.S. healthcare system, according to a recent commentary on the subject.

New PrEP Option Approved

In October 2019, the FDA approved a second drug combination, tenofovir alafenamide with emtricitabine (TAF/FTC), for PrEP in men who have sex with men, and transgender women. It is marketed as Descovy by Gilead Sciences, which also markets Truvada.

Safety and efficacy were demonstrated in an international trial including 5,387 participants that compared tenofovir alafenamide against tenofovir disoproxil fumarate, when used in combination with emtricitabine for PrEP. Data indicated that the tenofovir alafenamide combination was noninferior compared to the tenofovir disoproxil fumarate combination in prevention of HIV infection (incidence rate ratio 0.54; 95% confidence interval 0.23, 1.26).[2]

Data from the DISCOVER trial indicated no difference in drug-related adverse events of any grade (21% on TAF/FTC and 24% on TDF/FTC), serious adverse events that were drug related (0.1% to 0.2%) or in adverse events leading to drug discontinuation (1% vs. 2%). Findings suggested a difference in kidney function: By week 96, the mean glomerular filtration rate for TAF/FTC users had dropped by 0.6 milliliters per minute (mL/min), compared to 4.1 mL/min in TDF/FTC users.[2]

Gilead Sciences holds market exclusivity to TAF/FTC until 2022, and has requested a patent extension to 2025. If the generic version of TDF/FTC is perceived to be less safe, uptake of TAF/FTC would presumably rise — and bring cost ramifications, according to a new commentary co-authored by Krakower and **Julia Marcus**, PhD, assistant professor in the department of population medicine at Harvard Pilgrim Health Care Institute and Harvard Medical School.[3]

The authors pointed to a 2018 meta-analysis of 13 randomized clinical trials of PrEP in 15,678 participants, in which there were no significant differences in risk of grade 3/4 clinical adverse events or serious adverse events between TDF/FTC (or TDF) and the control. The meta-analysis also revealed no significant difference in risk of specific renal or bone adverse outcomes.[4]

> THE COST OF BRANDED TDF/FTC — AROUND $24,000 A YEAR — HAS CREATED BARRIERS TO ACCESS AT ALL LEVELS OF THE U.S. HEALTHCARE SYSTEM.

Prevention Is the Goal

How have costs of branded TDF/FTC affected HIV prevention efforts in the United States? According to Marcus, the cost of branded TDF/FTC — around $24,000 a year — has created barriers to PrEP access at all levels of the U.S. healthcare system.

Some insurance companies require prior authorization for PrEP in an effort to reduce costs, making it more difficult for patients to access PrEP, explains Marcus. Assistance programs can help cover out-of-pocket costs for PrEP users, but accessing these programs is so complex that some clinics have hired "PrEP navigators" to help patients sort through the paperwork, she says. If PrEP were more affordable, most people would be able to pay out of pocket without needing to navigate a complex system of payment assistance, she states.

"These cost barriers have a real impact on health outcomes. We've seen HIV transmissions occur when people have stopped taking PrEP because of gaps in their insurance coverage," explains Marcus. "We've surveyed people who recently contracted HIV to understand why they weren't taking PrEP before their HIV diagnosis, and found that cost was one of the most common reasons for not having used PrEP, or for discontinuing it." ■

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Scientists Make Important Step Toward HIV Cure

In two separate papers, scientists have documented how their efforts reversed HIV and simian immunodeficiency virus (SIV) latency in two animal models. Findings indicated progress toward an HIV cure.[1,2]

The research was conducted by investigators at the Collaboratory of AIDS Researchers for Eradication, based at the University of North Carolina at Chapel Hill and the Emory Consortium for Innovative AIDS Research in Nonhuman Primates. Both efforts were funded by the National Institutes of Health (NIH).

"A simple, safe, and scalable cure for HIV is an aspirational goal that, if achieved, would accelerate progress toward ending the HIV pandemic," **Anthony Fauci**, MD, director of the NIH's National Institute of Allergy and Infectious Diseases, said in a statement. "These new findings help sustain our cautious optimism that an HIV cure is possible."[3]

Scientists reactivated resting immune cells that were latently infected with HIV or SIV in cells in the bloodstream and a variety of animal tissues. The reactivated cells made copies of the virus, which could be neutralized by anti-HIV drugs and the immune system.[1,2]

New Compounds Under the Microscope

The persistence of viral reservoirs, where the HIV virus hides from the immune system, has made developing an HIV cure extremely difficult. These reservoirs consist of HIV-infected cells that contain genetic material capable of generating new virus particles if treatment is interrupted. These affected cells enter a resting state until activated to produce the virus. When the cells are resting, the immune system cannot recognize and kill them, rendering antiretroviral therapy ineffective.

Activating HIV reservoirs so therapeutic agents or an enhanced immune system can recognize and kill the infected cells has proven tricky. While laboratory efforts have worked well, testing in animal and human models have resulted in ineffective or toxic results.

Research efforts identified a compound called AZD5582, which belongs to a class of molecules that have been proven safe as experimental cancer therapies. In one experiment, researchers used 20 mice with human immune systems, infected them with HIV, and administered antiretroviral therapy to suppress the virus. Ten mice were injected with AZD5582, and the other 10 received placebo.

High levels of HIV RNA were detected in the blood of six of the AZD5582-treated mice within 48 hours, researchers reported. Scientists confirmed that the compound activated resting cells in the HIV reservoir throughout the treated mice without causing toxicity or immune system activation.[2]

Researchers also worked with 21 rhesus macaques, infecting them with SIV and providing suppressive antiretroviral therapy. More than a year after the therapy initiation, scientists administered weekly intravenous infusions of AZD5582 to 12 monkeys for either three or 10 weeks. Data suggested that the level of SIV increased in the blood of five of the nine monkeys (55%) that received 10 doses of AZD5582, and in none of the three monkeys that received fewer doses. Researchers reported that SIV RNA levels in resting immune cells from the monkeys' lymph nodes registered higher in animals treated with 10 doses of AZD5582 than in the nine monkeys that did not receive the compound.[2]

"It will be important to test other compounds in the same class of AZD5582 and possibly in combination with other latency reversal agents to determine which might be the best for testing in humans," says **Victor Garcia**, PhD, director of the International Center for the Advancement of Translational Science, professor of medicine and microbiology and immunology at the University of North Carolina at Chapel Hill School of Medicine. "If the results of these follow-up studies are successful, an early clinical trial may follow."

EXECUTIVE SUMMARY

In two separate papers, scientists have documented how their efforts reversed HIV and simian immunodeficiency virus latency in two animal models. Findings indicated progress toward an HIV cure.

- Investigators from the Collaboratory of AIDS Researchers for Eradication conducted the new research, funded by the National Institutes of Health.
- Research efforts identified a compound called AZD5582, which belongs to a class of molecules that have proven safe as experimental cancer therapeutics.

The authors of a different paper detailed how a combination of two agents affected the SIV reservoir in rhesus macaques and the HIV reservoir in mice with human immune systems when both animal models received antiretroviral therapy. The combination included an antibody, MT807R1, which depletes immune cells known as CD8+ T cells, and N-803, an engineered protein complex that activates certain immune cells to fight pathogens.

Scientists first infected 35 rhesus macaques with SIV and administered antiretroviral therapy, which suppressed the virus in 33 of the animals. Following at least one year after therapy initiation, researchers gave seven monkeys N-803, 14 monkeys MT807R1, and 14 monkeys the compound.

While N-803 alone had no effect on the SIV reservoir, data suggested MT807R1 alone led to a moderate increase in the level of SIV in the viral load. However, the combination of MT807R1 and N-803 led to a robust and persistent increase in the SIV viral load of all 14 animals, including the six in which fewer than three copies of SIV were detected before the experimental treatment began.[1]

"The exciting thing about these papers being published together are the concordance of the results in two animal models with both approaches, and the opening up of new avenues for research toward the goal of an HIV cure," **Ann Chahroudi**, MD, PhD, associate professor of pediatrics and director of the Center for Childhood Infections and Vaccines at Emory and Children's Healthcare of Atlanta.[4] ■

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Research Reinforces Importance of Tailoring Hormone Therapy

This year, more than 50 million U.S. women will be older than age 51 years, the mean age when menopause occurs. With an estimated 75% of women reporting symptoms, such as hot flashes or night sweats during the perimenopausal transition and beyond, what options are available to treat these symptoms?[1]

As women move through menopause, they are more likely to accumulate abdominal visceral fat, as well as fat around the heart.[2] Heart fat deposition has been linked to atherosclerosis progression, which also increases between perimenopause and postmenopause.[3]

A study examined the use of different oral and transdermal hormone therapy agents and the associations between heart fat accumulation and atherosclerosis progression. Data indicated that in comparison to transdermal estradiol patch, oral conjugated equine estrogen appeared to slow down the adverse effects of increasing paracardial adipose tissue on the progression of atherosclerosis.[4]

Researchers studied 467 healthy women ages 42-58 years who were enrolled in the Kronos Early Estrogen Prevention Study, a multicenter, randomized, placebo-controlled clinical trial. Participants enrolled between 2005 and 2008 and were followed for four years. Measuring carotid intima-media thickness allowed scientists to determine if there were associations between heart fat accumulation and progression of atherosclerosis. Epicardial and paracardial adipose tissue volumes were quantified by computed tomography.

Findings suggested that when compared with the estradiol patch, the oral conjugated equine estrogen appeared to slow the adverse effect of increasing paracardial adipose tissue on progression of atherosclerosis.[4]

Samar El Khoudary, PhD, MPH, associate professor of epidemiology at the University of Pittsburgh Graduate School of Public Health and lead author of the study, says more research is needed to help clinicians individualize hormone therapy prescription. "In our study, we could not determine if the beneficial effect of oral conjugated equine estrogens on how paracardial fat associates with

carotid intima-media thickness was due to conjugated equine estrogens or the oral route of administration," she explains. "Future research should address this question by comparing same estrogen type using different route of administration. Additional research is needed to assess the role of hormone therapy formulation, route of administration, and duration on cardiometabolic health."

The current study shows a "distinct effect" of hormone therapy on the link between heart fat deposits and atherosclerosis progression based on the type of estrogen or the route of administration used, says **Stephanie Faubion**, MD, MBA, medical director of the North American Menopause Society.

"Additional research is needed to allow clinicians to individualize hormone therapy prescribing to optimize benefit and minimize risk," says Faubion.

Educate Women on Heart Health

In both the prospective randomized Women's Health Initiative (WHI) and the Early Versus Late Intervention Trial, findings indicated that starting hormone treatment within five to 10 years of menopause can offer cardioprotection in postmenopausal women without adverse effects.[5] Further analysis of the WHI data suggested that beginning hormone treatment within the first decade after menopause is safe and effective.[6]

Educate women on the key risk factors for heart disease: high blood pressure, high low-density lipoprotein (LDL) cholesterol, and smoking. Explain that other conditions, such as diabetes, being overweight or obese, eating an unhealthy diet, physical inactivity, and drinking too much alcohol, can add to risk for heart problems.

Suggest such lifestyle changes as smoking cessation; eating more fruits, vegetables, grains, beans, low-fat dairy products, fish, and lean meats and poultry; weight reduction; exercising at least 30 minutes most days; and controlling blood pressure, using medication if necessary.

Review heart attack symptoms with patients, and explain that heart attacks in women often show different symptoms than in men. Tell women that they should seek medical care as soon as possible if one or more of the following symptoms are present:

- chest pain, pressure, or squeezing;
- pain in the jaw, arms, back, or neck;
- extreme fatigue;
- shortness of breath;
- nausea;
- unusual sweating;
- upper stomach pain. ■

EXECUTIVE SUMMARY

Data from research that examined the use of different oral and transdermal hormone therapy agents and their associations between heart fat accumulation and atherosclerosis progression indicated that in comparison to transdermal estradiol patch, oral conjugated equine estrogen appears to slow the adverse effects of increasing paracardial adipose tissue on the progression of atherosclerosis.

- Women in menopause are more likely to accumulate abdominal visceral fat, as well as fat deposition around the heart. Heart fat deposition has been linked to atherosclerosis progression, which also increases between perimenopause and postmenopause.

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Testing Detects Hormone Changes Signaling Menopause

More than 50 million U.S. women this year will be older than 51.[1] Since menopause occurs at an average age of 52 years, how can clinicians help women better determine their final menstrual period?

Results of a new study established that levels of anti-Müllerian hormone (AMH) can predict when a woman's final menstrual period will occur.[2] By measuring AMH levels, clinicians have an indicator of how many eggs a woman has remaining. Women are born with a finite supply of eggs that diminishes as menopause is approached.

Data come from a prospective longitudinal cohort study conducted as part of the Study of Women's Health Across the Nation (SWAN). Scientists examined blood tests from 1,537 women ages 42-63 years. While the long-term SWAN study monitored women's health changes as they moved through the menopausal transition, for the current study, participants' blood samples were tested for AMH levels as well as follicle-stimulating hormone.

To measure the participants' AMH levels, scientists used a more sensitive test than what previously had been available. With the enhanced sensitivity, scientists predicted the final menstrual period timing within 12 to 24 months in women in their late 40s and early 50s.[2]

The results were part of the scientific evidence presented to the FDA for the 2018 approval of MenoCheck, an assay kit used to determine menopausal status in women ages 42-62. The assay offers adequate sensitivity to measure declining AMH concentrations in women who are entering menopause.

Which women may benefit from knowing their menopausal status? While it may not be necessary to test all women, there are several instances where it can be helpful for a woman and her healthcare provider to forecast her final menstrual period with greater precision, says **Nanette Santoro**, MD, professor and E. Stewart Taylor Chair of Obstetrics and Gynecology at the University of Colorado School of Medicine.

For example, a woman who does not experience gynecological problems, is in a monogamous relationship with a sterile man, and notes a late onset of her menopause with minimal symptoms will not be motivated to answer this question in advance, notes Santoro. However, Santoro, who served as co-lead author of the study, lists several conditions where testing may be advantageous:

• **Contraceptive decisions.** Santoro offers the example of a 50-year-old woman with a levonorgestrel intrauterine device (IUD) who is looking to replace it in two years. With AMH testing, she may determine that she is highly likely to experience her final menses before then and will not need to replace the IUD, based on a very low AMH level. Conversely, a 48-year-old woman who has a very high AMH, but the same IUD and timing issues would be unlikely to experience her final menses, and should continue her IUD.

"Because both [levonorgestrel] IUD and implant methods do not appreciably suppress the production of follicle-stimulating hormone [FSH] and luteinizing hormone [LH], but may change the menstrual pattern, these women cannot rely on menstrual patterns to make this prediction. An AMH is helpful," says Santoro.

Clinicians should remember an important caveat: Since FSH, LH, and AMH are suppressed in women taking combined hormonal contraception, the test will not be predictive. It cannot be used to answer the question, "When can I stop my birth control pills?," but it can be used with these other methods, Santoro advises.

• **Surgical decisions.** A woman with heavy menstrual bleeding from fibroids, adenomyosis, or idiopathic origin stands to benefit from knowing how much longer she has to deal with her symptoms, says Santoro.

EXECUTIVE SUMMARY

Results of a new study established that levels of anti-Müllerian hormone (AMH) can predict when a woman's final menstrual period will occur. By measuring AMH levels, clinicians have an indicator of how many eggs a woman has remaining. Women are born with a finite supply of eggs that diminishes as menopause is approached.

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"If she is 50, with a very low AMH, she may just want to temporize with medical management to get to menopause," Santoro explains. "However, if she is 48 with a high AMH, she will know that she is facing years more of disruptive menstrual periods and may opt for surgery — hysterectomy, myomectomy, or endometrial ablation, depending on the exact problem."

• **Accurate diagnosis.** Not all cases of amenorrhea in women in their 40s and 50s are due to menopause, says Santoro. Some cases are from pituitary tumors and other rare conditions. If the signs and symptoms are atypical, an AMH level can help to distinguish between menopause and other causes, she states. ■

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Ethics Curriculum Feasible for OB/GYN Faculty

Much ethics education focuses on students and residents, but practicing physicians also need ethics expertise. An ethics and professional curriculum was piloted for faculty in obstetrics and gynecology.[1]

"Our motivation was the awareness that faculty model ethical knowledge, behavior, and care formally, informally, and via the hidden curriculum," says **Kavita Shah Arora**, MD, MBE, MS, one of the study's authors.

The goal was to fill gaps in ethics education. Twenty-eight faculty members attended a single four-hour session. Participants reported less burnout. "We were happy to see that our curriculum was both feasible and well-received. Faculty are looking for this information," says Arora, an associate professor of reproductive biology and bioethics at Case Western Reserve University.

While efforts have been made to educate trainees, there has been a relative lack of ethics education focused on medical faculty. "Further work is necessary to assess whether we also raised knowledge in ethics and impacted use of ethics consultative services," Arora adds.

Ethicists who work alongside obstetrician-gynecologists should consider offering these routine educational opportunities, according to **David I. Shalowitz**, MD, MSHP:

• Review common ethical issues (advance care directives, informed consent for procedures, or whether sale of nonmedical products is permissible in the clinic);

• Give updates on intersections between the law and ethics;

• Discuss cases that clinicians have found particularly challenging.

"Obstetrician-gynecologists routinely encounter ethical challenges during clinical care," notes Shalowitz, assistant professor of gynecologic oncology at Wake Forest Baptist Health.

Some of these issues are addressed by the Committee on Ethics of the American College of Obstetricians and Gynecologists. This provides adequate guidance in most circumstances, Shalowitz says. "However, in some cases, uncertainty may remain, in which case an ethics consultant may provide much-needed clarity," he explains.

Continuing ethics education is vital for practicing physicians, "especially in our field," says **Ginny Ryan**, MD, MA (Bioethics), an associate professor in University of Iowa's department of obstetrics and gynecology. "Medical students I work with consistently rank obstetrics and gynecology as the most ethically fraught experience they have on their rotations," she reports.

Students find it challenging to consider pregnant women as separate from the fetus. "Students also struggle with issues surrounding abortion, pelvic exams on anesthetized patients, reproductive rights, and the lack of availability of infertility care," Ryan adds.[2]

Hospital leaders also can support providers by encouraging continuing ethics education and conference attendance. "Leaders can look into hosting their own conferences or roundtables to address locally or regionally pertinent ethics issues," Ryan suggests. ■

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CONTRACEPTIVE TECHNOLOGY UPDATE®

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.

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CME/CE QUESTIONS

1. **The copper T 380A intrauterine device is designed to be used in women whose uterine cavities sound to what depth?**

   a. 3-5 cm
   b. 4-6 cm
   c. 5-7 cm
   d. 6-9 cm

2. **Elagolix, used in the treatment of endometriosis pain, belongs in what class of medications?**

   a. Steroidogenesis inhibitor
   b. Gonadotropin-releasing hormone antagonist
   c. Androgen antagonist
   d. Selective estrogen receptor modulator

3. **What is the drug combination in PrEP medication Descovy?**

   a. Tenofovir alafenamide/emtricitabine
   b. Bictegravir/emtricitabine/tenofovir alafenamide
   c. Emtricitabine/rilpivirine/tenofovir alafenamide
   d. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

4. **The MenoCheck test measures which of the following to predict when a woman's final menstrual period will occur?**

   a. Dimethandrolone
   b. Follicle-stimulating hormone
   c. Anti-Müllerian hormone
   d. Luteinizing hormone

CME/CE OBJECTIVES

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

1. identify clinical, legal, or scientific issues related to development and provisions of contraceptive technology or other reproductive services;
2. describe how those issues affect services and patient care;
3. integrate practical solutions to problems and information into daily practices, according to advice from nationally recognized family planning experts;
4. provide practical information that is evidence-based to help clinicians deliver contraceptives sensitively and effectively.