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INSIDE

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Success with Teen Pregnancy Rate, But There Is More Work Left to Do

While birth rates fall, important gaps remain for many communities

Just-published data indicate that births among Hispanic and black teens have dropped by almost half since 2006, which mirrors a substantial national decline. Births to all American teenagers have dropped more than 40% within the past decade.[1]

Although the teen birth rates among blacks and Hispanics have fallen faster than among whites, the racial disparity in adolescent childbearing remains wide. According to the data from the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC), nationally, the teen birth rate declined 41% overall (from 41.1 per 1,000 to 24.2 per 1,000). The largest decline occurred among Hispanics (51%, from 77.4 to 38.0), followed by blacks (44%, from 61.9 to 34.9), and then whites (35%, from 26.7 to 17.3). Correspondingly, the birth rate ratio for Hispanic teens and black teens compared with white teens declined from 2.9 to 2.2 and from 2.3 to 2.0, respectively.[1]

"THE UNITED STATES HAS MADE REMARKABLE PROGRESS ... BUT ... TOO MANY AMERICAN TEENS ARE STILL HAVING BABIES."
— TOM FRIEDEN, MD, MPH, CDC

Researchers looked at national- and state-level data from the National Vital Statistics System (NVSS) to examine trends in births to American teens ages 15-19 from 2006 to 2014. County-level NVSS data for 2013 and 2014 offered a point-in-time picture of local birth rates. To better understand the relationship between key social and economic factors and teen birth rates, researchers also analyzed data from the American Community Survey between 2010 and 2014. Here is what they discovered in terms of key community- and state-level patterns:

- In some states, birth rates among

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EDITORIAL QUESTIONS OR COMMENTS?
Joy Daugherty Dickinson (404) 262-5410
Joy.Dickinson@AHCMedia.com

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EDITOR: Rebecca Bowers
EXECUTIVE EDITOR: Joy Daugherty Dickinson
CONTINUING EDUCATION & EDITORIAL DIRECTOR: Lee Landenberger

Hispanic and black teens were more than three times as high as those of whites. An example is New Jersey, where the teen birth rate among whites (4.8 per 1,000 teen-agers ages 15-19) was well below the national rate for this group (18.0). While New Jersey teen birth rates among blacks (27.4) and Hispanics (31.3) also were lower than the national rates for these groups (blacks: 37.0; Hispanics: 39.8), they were approximately sixfold to sevenfold higher than the rate for whites.

• Higher unemployment and lower income and education are more common in communities with the highest teen birth rates, regardless of race.

• In some states with low overall birth rates, pockets of high birth rates exist in some counties.

• Counties with higher teen birth rates were clustered in southern and southwestern states.[1]

"The United States has made remarkable progress in reducing both teen pregnancy and racial and ethnic differences, but the reality is, too many American teens are still having babies," says **Tom Frieden**, MD, MPH, CDC director. "By better understanding the many factors that contribute to teen pregnancy, we can better design, implement, evaluate, and improve prevention interventions and further reduce disparities."

The CDC is working on several fronts to prevent teen pregnancy. One key component of its work is encouraging community-centered efforts. Between 2010 and 2015, the CDC and the Department of Health and Human Services' Office of Adolescent Health collaborated to demonstrate the effectiveness of innovative, multicomponent, communitywide initiatives in reducing rates of teen pregnancy and births in communities with the highest rates, with a focus on reaching African American and Latino or Hispanic teens ages 15-19.

Preliminary outcome data indicate that the communitywide initiatives have been successful. Each community increased the number of teens who received evidence-based teen pregnancy prevention interventions and reproductive health services, as well as the percentage of teens who received moderately or highly effective contraceptive

EXECUTIVE SUMMARY

New data indicate that births among Hispanic and black teens have dropped by almost half since 2006, which mirrors a substantial national decline. Births to all American teens have dropped more than 40% within the past decade.

• Although the teen birth rates among blacks and Hispanics have fallen faster than among whites, the racial disparity in adolescent childbearing remains wide.

• Federal efforts are focusing on community-wide initiatives. Preliminary data indicate that such efforts have increased the number of teens who received evidence-based teen pregnancy prevention interventions and reproductive health services, as well as raised the percentage of teens who received moderately or highly effective contraceptive methods, including long-acting reversible contraception.

methods, including long-acting reversible contraception (LARC). Many of those strategies are being implemented across the United States through 84 five-year teen pregnancy prevention grants for programs supported through the Office on Adolescent Health.

The new data underscore that the solution to the national teen pregnancy problem is not going to be a "one-size-fits-all" solution, because teen birth rates vary greatly across state lines and even within states, says **Lisa Romero**, DrPH, a health scientist in CDC's Division of Reproductive Health and lead author of the analysis.

"We can ensure the success of teen pregnancy prevention efforts by capitalizing on the expertise of our state and local public health colleagues," says Romero. "Together, we can work to implement proven prevention programs that take into account unique, local needs."

"Teen-friendly" care

How can clinicians enhance their practice for the best in "teen-friendly" care? **Melissa Kottke**, MD, MPH, MBA, associate professor at Emory University and director of the Jane Fonda Center for Adolescent Reproductive Health and medical director of the Grady Teen Clinic, all in Atlanta, offered advice at the most recent *Contraceptive Technology* conferences.[2]

What barriers prevent adolescents from seeking reproductive health care? According to Kottke, these include:

- inaccessible locations and/or limited services;
- limited office hours;
- lack of money, insurance, and transportation;
- poor communication and/or insensitive attitudes by providers;
- lack of provider knowledge and skills;
- perceived lack of confidentiality and restrictions (parental consent/notification).

Clinicians need to find ways to make it easier for teens, says Kottke. She points to a free infographic from the CDC that outlines a teen-friendly reproductive health visit. *(The infographic is available online at http://1.usa.gov/1QnAdLh).*

Ease teens' fears when it comes to a provider encounter. Let them know that a pelvic exam is not a prerequisite for starting contraception. It is necessary only if a woman is having symptoms, says Kottke. Screening for sexually transmitted infections can be done via a urine test or a vaginal swab, she points out. National guidance calls for cervical cancer screenings to begin at age 21.

One way to provide teen-friendly options is to offer LARCs for adolescent birth control, notes Kottke. Intrauterine contraceptives and the contraceptive implant offer top-tier pregnancy prevention, and their use is supported by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Both national organizations have issued policy statements affirming that LARC methods are safe, effective, and appropriate options for teens.[3,4] (Contraceptive Technology Update *reported on the subject. See the January 2014 article, "LARC methods: 7 things you need to know," which is available at http://bit.ly/1T73i2V.)*

When talking with adolescent females about sex, build a foundation that rests on sexuality, self, relationships, and the future, not just sex, advises Kottke. Start with her current context, strengths, and goals for the future, then follow up on the partner. Encourage discussions, and use role-play during counseling. Be aware of judgment and jargon, and use open-ended questions. Motivational interviewing techniques work well with teens, says Kottke. These techniques place the focus of the interview on future goals, belief in the adolescent's capacity to change, and engagement of the adolescent in adopting health-promoting behaviors. *(To obtain more information on motivational interviewing, see the article "Use motivational interviewing with teens," December 2014* Contraceptive Technology Update, *which can be accessed online at http://bit.ly/1Yq2wfr.)*

Adolescence is a time of rapid change, notes Kottke. Provision of contraception should not be limited by age, she states. "Supporting overall sexual health of young people often involves access, removing barriers, including those of historical practice patterns, and discussion," Kottke states. *(In an upcoming issue,* Contraceptive Technology Update *will examine some of the reasons teen births are the lowest in the history of the United States.)*

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Update on Contraceptive Implant — What Family Planners Need to Know

The contraceptive implant Nexplanon (Merck, Whitehouse Station, NJ) offers top-tier effectiveness against unintended pregnancy. How can you identify appropriate candidates, present counseling tips on the contraceptive and noncontraceptive benefits, and recognize and treat side effects and rare complications?

The implant provides "unsurpassed contraceptive efficacy," says **Anita Nelson**, MD, professor emeritus in the Obstetrics and Gynecology Department at the David Geffen School of Medicine at the University of California in Los Angeles. Nelson presented on the subject at the 2016 *Contraceptive Technology* conference.[1]

The implant, a single rod (4 cm by 2 mm) made of ethylene vinyl acetate, contains 68 mg of etonogestrel. Its mechanism of action is through ovulation suppression and thickened cervical mucus, notes Nelson. In U.S. trials, just six pregnancies were recorded in 20,648 cycles, she states.

Nexplanon, as well as its forerunner, Implanon, is marketed with a duration of action of three years. However, data indicate that the device is effective for longer than that time period. Three studies in which 275 women used Implanon for longer than three years found no pregnancies during the fourth year of use.[2]

This research was corroborated by findings published in 2015 by researchers at the Washington University School of Medicine in St. Louis. Their initial analysis of data indicates that hormonal intrauterine devices (IUDs) and contraceptive implants remain highly effective one year beyond their approved duration of use.[3] *(*Contraceptive Technology Update *reported on the data. Readers can see the May 2015 article, "Intrauterine device and implant are effective beyond use approved by the FDA," which can be accessed online at http://bit.ly/1rKxWTj.)*

Who can use method?

The *U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC)* lists few medical conditions that contraindicate the use of implants (Category 3 or 4):

- unexplained, unevaluated abnormal vaginal bleeding;
- systemic lupus erythematosus or unknown antiphospholipid antibodies;
- severe (decompensated) cirrhosis;
- benign or malignant liver tumor;
- current or past breast cancer;
- use of ritonavir-boosted protease inhibitors, certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine), rifampicin, or rifabutin.[4]

There are no restrictions on implant use based on age, smoking, hypertension, migraine without aura, uterine fibroids, diabetes, gallbladder disease, or sickle cell anemia.[2] No examinations or laboratory tests are needed to determine whether a woman is eligible to use implants, except in women with lupus.[2]

Insertion of an implant may occur at any time during the menstrual cycle as long as pregnancy may be reasonably excluded. Backup methods of contraception, such as use of a condom, should be used for seven days after insertion, unless the device is inserted within five days of initiating menses, immediately after childbirth or after abortion, or immediately upon switching from another hormonal contraceptive.[5]

If switching from use of an intrauterine device not near menses, Nelson advises abstinence/second method for seven days prior to removal and implant placement.

How about bleeding?

Like all progestin-only methods, Nexplanon causes vaginal bleeding in a large proportion of women. The bleeding pattern experienced during the first three months is

EXECUTIVE SUMMARY

The contraceptive implant Nexplanon and its forerunner, Implanon, offer top-tier effectiveness against unintended pregnancy. Clinicians need to be able to identify appropriate candidates, present counseling tips on the contraceptive and noncontraceptive benefits, and recognize and treat side effects and rare complications.

- Nexplanon, as well as Implanon, is labeled with a duration of action of three years. However, data from several sources indicate that the device is effective for longer than that time period.
- The *U.S. Medical Eligibility Criteria for Contraceptive Use* lists few medical conditions that contraindicate the use of implants. There are no restrictions on implant use based on age, smoking, hypertension, migraine without aura, uterine fibroids, diabetes, gallbladder disease, or sickle cell anemia.

broadly predictive of future bleeding patterns for many women. Effective preinsertion counseling on the possible changes in bleeding patterns may improve continuation rates, research indicates. Half of women with unfavorable patterns in the first three cycles will improve with time.[6]

Between 6% and 12% of implant users in contraceptive studies report weight gain; however, few discontinue the implant due to weight change.[7] Studies suggest the overall implant removal rate because of weight gain varies from 3% to 7%.[7]

Research indicates that overall, 15% of women using implants report acne; however, only 1% had the implant removed for this reason.[8]

The message for clinicians is that implants and intrauterine devices provide top-tier contraception, says Nelson. Pills, patches, rings, and the contraceptive injection have 21 times higher pregnancy risk, she notes.

"Eliminate all barriers to access," says Nelson. "Counsel effectively, and provide method same day as visit."

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Data Suggest Hormonal Therapy Doesn't Increase VTE Risk in Women on Anticoagulant Therapy

Women on anticoagulant therapy can take estrogen-containing contraception or hormone therapy without an increased risk of blood clots or uterine bleeding, findings from a recent study suggest.[1]

Clinicians are reluctant to prescribe estrogen-containing contraceptives or postmenopausal hormone therapy to women who use anticoagulants for venous thromboembolism (VTE) due to the documented increased risk of VTE with these hormonal agents.[2-4] Product labeling for combined oral contraceptives, as a class, generally indicates that use is contraindicated in patients with an active or prior VTE event, although no reference is made to the concomitant use with anticoagulation.[1]

To answer the question of whether women can safely take hormone-containing medication with anticoagulants, **Ida Martinelli**, MD, PhD, head of the Thrombosis Center at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center in Milan, and fellow researchers compared the incidences of recurrent blood clots and abnormal uterine bleeding in 1,888 women who received blood thinners with and without concurrent hormone therapy. To perform the analysis, the scientists looked at patient data from the EINSTEIN deep vein thrombosis (DVT) and pulmonary embolism (PE) study.[5-6] The original research was designed to evaluate the safety and efficacy of two anticoagulants: the new direct oral anticoagulant, rivaroxaban, and the current standard of care, a low-molecular-weight heparin (enoxaparin) followed by a vitamin K antagonist (VKA). Women of childbearing age were advised to use adequate methods of contraception to avoid birth defects.

Of the total number of women in the analysis, 1,413 used no hormonal contraception, and 475 used some type of hormone therapy. Hormone therapy included estrogen-only pills, combined estrogen-progestin contraceptives (pills, patches, vaginal rings, and injectables), and progestin-only contraceptives (pills, implants, injectables, and intrauterine devices). Study participants were questioned

about symptoms or signs of recurrent blood clots and bleeding, including uterine bleeding, during each follow-up visit.

Data indicate seven recurrent blood clot events occurred while patients were using hormone therapy, while 38 events occurred during a time when patients weren't using hormone therapy. Researchers conclude that women on blood thinners and hormone therapy experienced recurrent blood clots at a rate of 3.7% per year. In contrast, those not on hormone therapy had a recurrence rate of 4.7% per year. Also, the incidence of abnormal uterine bleeding in those on hormonal therapy was 22.5%, compared to 21.4% in women not using hormone therapy. The similar incidence of blood clots and abnormal uterine bleeding in women who did and did not receive hormone therapy suggests that the combined use of these therapies is safe.[1]

More frequent bleeding

Study findings indicate that abnormal uterine bleeding occurred more frequently with rivaroxaban than with enoxaparin/VKA.

The bleeding rate was estimated at 29.8% per year for patients on rivaroxaban and 15.5% per year in the enoxaparin/VKA group. Researchers note the need for further studies on the oral anticoagulant, which often is preferred for its convenience over subcutaneous doses of enoxaparin/VKA.[1]

"For the first time, we demonstrate that women suffering from blood clots can safely take hormone-containing contraceptives or hormone replacement therapy with anticoagulants, providing women the freedom to choose the method of birth control and other hormone-containing medications they prefer," says Martinelli. "While further investigation is needed to evaluate the inconvenience of abnormal uterine bleeding with rivaroxaban and the other direct oral anticoagulants, these results dispel former misconceptions and should allow clinicians to confidently treat their patients who take blood thinners and hormones concurrently."

What is your call?

The *U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC)* discourages use of combination contraceptives in women with a history of VTE on anticoagulation.[7] However, it also notes that when a hormonal contraceptive is used not solely to prevent pregnancy, but also to prevent/treat gynecologic problems (which include not only heavy menstrual bleeding but also post-ovulatory hemorrhage), the risk/benefit ratio should be considered on a case-by-case basis.

Andrew Kaunitz, MD, University of Florida Research Foundation professor and associate chairman of the Department of Obstetrics and Gynecology at the University of Florida College of Medicine – Jacksonville, says, "Unintended pregnancy among women with a history of VTE represents a high-risk condition; furthermore, vitamin K antagonists are teratogens. These observations underscore the importance of the authors' findings that among women with a history of VTE who are currently anticoagulated, hormonal contraception does not increase recurrent VTE risk."

Because the procoagulant effects of estrogen may not resolve for a number of weeks after stopping the medication, clinicians maintaining anticoagulated patients on combination contracep-tives should stop such methods some six weeks prior to discontinuing anticoagulation, says Kaunitz.

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Medicaid Pushes Forward on Family Planning

By ***Adam Sonfield***
Senior Public Policy Associate
Guttmacher Institute
Washington, DC

With the end of the Obama administration rapidly approaching, federal agencies have stepped up their efforts to finalize long-brewing regulations and guidance. The Centers for Medicare and Medicaid Services (CMS) has been particularly active. In April 2016, the agency issued three documents that all have considerable importance for family planning services and providers under Medicaid.

On April 8, CMS issued a long-promised informational bulletin from its Maternal and Infant Health Initiative, which has made increasing access to and use of effective methods of contraception one of its two main objectives.[1] The bulletin details approaches from 14 states to promote the coverage and availability of long-acting reversible contraceptives (LARCs), namely intrauterine devices and contraceptive implants. (The 14 states are Alabama, California, Colorado, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Montana, New Mexico, New York, South Carolina, and Texas.)

The approaches are designed to overcome a cluster of commonly reported obstacles to making LARC methods available for Medicaid enrollees. For example, states have taken steps to ensure that all necessary contraceptive services are covered (including counseling, and device insertion, removal, replacement, and reinsertion) and to eliminate prior authorization and similar coverage limits.

States also have worked to improve reimbursement for LARCs and other methods, to help providers offer the full range of choices. That work has included unbundling payment for LARCs from other labor and delivery services and allowing providers to bill for an office visit and a device insertion on the same day. Finally, states have worked with manufacturers to address issues related to supply management, including the upfront costs of keeping expensive devices in stock.

Blocking abortion attacks

CMS' next big move was an April 19 letter to state Medicaid directors that put states on notice that cutting providers in good standing — specifically, family planning providers — out of their Medicaid programs will run them afoul of federal law.[2]

This guidance represents a forceful rejection of states' increasingly widespread attempts to deny Medicaid funding from Planned Parenthood health centers and other providers that offer abortion services or are affiliated with a provider that does so. CMS' letter makes it clear that states do not have the legal authority to oust providers from their Medicaid networks without legitimate evidence of wrongdoing; such actions unlawfully limit Medicaid beneficiaries' right to obtain care from a qualified, willing provider of their choosing.

The letter further highlights that Medicaid's provision for "free choice of provider" has long applied specifically to family planning, and it explicitly says that beneficiaries cannot be denied access to a provider solely because they offer the "full range of legally permissible gynecological and obstetric care, including abortion services." More generally, CMS makes it clear that states may not target providers for reasons beyond their ability to provide services and properly bill for them, and that the "failure of a state to apply otherwise reasonable standards in an evenhanded manner may suggest such targeting." Multiple federal courts have agreed with CMS on this longstanding interpretation of federal law.

CMS followed up on April 25 with its sweeping final regulations on Medicaid managed care plans, which are privately run plans through which most Medicaid enrollees receive their coverage, including almost all of those newly eligible under the Affordable Care Act's Medicaid expansion.[3] The regulations initially were proposed in May 2015 and mark the most extensive update in nearly 15 years. They address access to family planning and other reproductive health services in numerous ways.

Notably, managed care plans are explicitly barred from imposing utilization controls that interfere with Medicaid enrollees' freedom to choose a contraceptive method, specifically including prior authorization requirements or so-called step therapy (requiring that enrollees first try one method, such as the Pill, before trying the method of their choice, such as an intrauterine device).

A major piece of the regulations sets new standards to ensure that managed care plans' provider networks, including their network

of obstetrician-gynecologists, be comprehensive enough to meet their enrollees' needs.

Separately, plans will need to demonstrate that they have included sufficient family planning providers in their networks to ensure timely access to care. As CMS notes, "use of network providers facilitates claims payment, helps enrollees locate providers more easily, and improves care coordination."

The regulations also clarify a "direct access" requirement: that Medicaid enrollees be allowed to receive care from a women's health specialist without a referral. They require plans and states to inform enrollees about specific rights, including the freedom to obtain care from the family planning provider of their choice, even if their managed care plan otherwise restricts coverage to in-network providers. States are reminded of their obligation to ensure that Medicaid enrollees can access all covered information and services, even when providers or managed care plans have religious/moral objections.

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A Low-Dose Estrogen Capsule Examined as Possibility for Vaginal Atrophy

About 32 million postmenopausal women in the United States are affected by vulvar and vaginal atrophy, which can cause painful sexual activity and urination, as well as vaginal dryness, itching, and irritation.[1] Recent data presented at ENDO 2016, the annual meeting of the Endocrine Society, suggests an investigational low-dose vaginal estrogen capsule may help relieve such symptoms.[2,3]

Vulvar and vaginal atrophy is chronic and progressive. Unlike vasomotor symptoms, it will not resolve with time and without treatment. Left untreated, these symptoms not only can cause discomfort, but also can negatively impact women's quality of life, including sexual relationships and emotional well-being.[4]

A recent study recruited women ages 55 and older from primary care offices and senior centers to answer questions about common symptoms after menopause. Results indicate that vulvar and vaginal symptoms such as itching, burning, stinging, pain, irritation, dryness, discharge, or odor, were very common. More than half of the women (51%) said they had one or more of these symptoms; 40% of women with symptoms said the symptoms posed emotional problems, and 33% said they had an impact on their lifestyle.[5]

There is an "unmet need" for postmenopausal women to have regular gynecologic visits during which questions can be asked about vaginal and urinary health problems and assessment can be made to determine the presence of these symptoms, says **JoAnn Pinkerton**, MD, NCMP, executive director of the North American Menopause Society.

"Women need to tell their healthcare providers about their genitourinary symptoms, and providers need to ask," states Pinkerton.

To help providers and patients more comfortably discuss the changes often associated with menopause, the North American Menopause Society and the International Society for the Study of Women's Sexual Health in 2014 developed the term "genitourinary syndrome of menopause." The term defines "a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder," and includes genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections.[6]

The research presented at the ENDO 2016 conference looked at TX-004HR, an investigational drug containing the estrogen 17β-estradiol.

The drug, under development by TherapeuticsMD of Boca Raton, FL, is in clinical trials and is not available to the general public.

TherapeuticsMD conducted the double-blind, randomized Phase 3 clinical trial comparing three doses (4, 10, and 25 mcg) of TX-004HR with placebo in 764 postmenopausal women ages 40-75 in 105 medical centers in the United States and Canada. The women in the study received vaginal softgel capsules containing one of the three doses of TX-004HR or placebo, once daily for two weeks, then twice weekly for 10 weeks.

Study results suggest that within two weeks, at all doses, vaginal cells and vaginal pH improved, compared with placebo. Superficial and parabasal vaginal cell improvement was found at baseline and at two, six, eight, and 12 weeks. Study findings suggest vaginal pH returned to premenopausal levels. Dyspareunia, vaginal dryness, and irritation also showed improvement. Scientists report that TX-004HR did not, on average, increase blood levels of estradiol outside the normal postmenopausal range. The treatment was well-tolerated. No treatment-related serious adverse events were reported, and no clinically significant differences in any adverse events or treatment-related serious adverse events were found between TX-004HR and placebo.[2,3]

The current treatment for genito-urinary syndrome of menopause is low-dose estrogen in the vagina through creams, pills, or rings. TherapeuticsMD says it plans to use its trial data for TX-004HR, conditionally branded as Yuvvexy, as the basis for a New Drug Application to the FDA.

"This study provides a new easy-to-use option for vulvar and vaginal atrophy, for which only about 7% of women are currently treated with a prescription product," said lead author **Ginger Constantine,** MD, president and CEO of EndoRheum Consultants in Malvern, PA, in a statement accompanying the study presentation. "Health care providers and their patients may soon have an additional safe and effective product for a very untreated condition."

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ABSTRACT & COMMENTARY

Screening for Ovarian Cancer: Helpful or Harmful?

By ***Molly A. Brewer****, DVM, MD, MS*
Professor and Chair, Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
University of Connecticut Health Center, Farmingham

SOURCE: Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. *Lancet* 2016; 387(10022):945-956.

Ovarian cancer has the highest mortality of any of the gynecologic cancers. Due to the poor prognosis associated with this disease, researchers have been searching for 50 years for an early detection tool. Most women diagnosed with high-grade epithelial ovarian cancer will be diagnosed with Stage III or IV disease with a mortality of at least 70% over five years. The mortality has not changed appreciably in 50 years, despite multiple studies testing

treatment combinations of surgery, chemotherapy, and newer targeted therapies. The first screening tool, CA125, a glycoprotein that is secreted by ovarian cancer cells and can be detected in serum, initially was described in 1983 by Robert Bast, MD, as a tool to monitor response to treatment for ovarian cancer and not as a screening tool for the detection of early cancer.[1] Soon physicians extrapolated the use of serum CA125 for screening, and they paired this with pelvic ultrasound. However, in 1994, a National Institutes of Health consensus statement cautioned against routine use of CA125 and pelvic ultrasound in the general population and recommended using these tests for screening only in high-risk women.[2] Despite the lack of evidence that screening saves lives or alters disease prognosis in low-risk women, there have been multiple studies evaluating serum markers with or without ultrasound in women with a pelvic mass,[3] premenopausal women,[4] and postmenopausal women.[5-7] Given that the baseline lifetime risk for a low-risk woman to develop ovarian cancer is 1.5-1.7%, the positive predictive value (the probability that a positive test could predict the presence of disease) of any screening test will be low. In the case of ovarian cancer screening, a low positive predictive value would result in many unnecessary surgeries.

In 2015, Jacobs et al published results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which enrolled 202,638 low-risk postmenopausal women who were randomized to multimodal screening (MMS), ultrasound alone, or no screening.[8] The primary outcome of the trial was the comparison of mortality from ovarian cancer between the three cohorts. The researchers had planned to stop the study seven years after randomization, but the mortality in the no-screening group was lower than expected, so they extended the study to 14 years. Using their initial statistical approach, the authors found no statistically significant difference between the groups when MMS was compared to no screen or ultrasound alone was compared to no screen. Given that they assumed a 30% difference in mortality a priori and failed to see this difference initially suggests that they were underpowered to detect a difference and overestimated the screening potential of MMS. When they removed the cases of ovarian cancer that were present at the time of randomization (prevalent cases), there was 28% less mortality in the MMS group compared to the no screen group in years 7-14, which was a statistically significant difference. It is not clear what the improvement in mortality would be if women were screened their entire postmenopausal lifetime. To translate these data into real numbers, of the approximately 200,000 women screened during 14 years, there were 1,025 ovarian cancers. They reduced the mortality from 580/100,000 women in the no-screen group to 390/100,000 women in the MMS group prior to removing the prevalent cases, a difference of 180 women. After the prevalent cancer cases were removed, the mortality was reduced from 450/100,000 women to 250/100,000 women, a difference of 200 women over 14 years. There were 483/50,000 unnecessary surgeries in the MMS group and 1,638/50,000 unnecessary surgeries in the ultrasound group.

COMMENTARY

So how do we interpret these data, and how should we incorporate these results into our practice? This is the first ovarian cancer screening study to show a reduction in mortality with screening. The Prostate, Lung, Colorectal and Ovarian (PLCO) study showed no change in mortality with screening low-risk postmenopausal women for ovarian cancer.[9] However, there were significant differences in these two studies: The PLCO study only used a CA125 cutoff, and the UKCTOCS used their Risk of Ovarian Cancer Algorithm (ROCA) in the MMS group. This group has worked for more than 20 years to understand trends in CA125 and to mathematically describe the pattern of CA125 variability in postmenopausal women that predicts ovarian cancer. That being said, the question must be posed: Should we be screening low-risk women for ovarian cancer?

Screening for type 2 diabetes makes economic sense, given the frequency of this disease. Based on Centers for Disease Control and Prevention data, the prevalence is approximately 9.3% or 29.1 million people in the United States and is as high as 25% in people older than 60 years of age.[10] The incidence in the population older than 20 years of age is 7.8%/1,000 people screened. Many of the complications of type 2 diabetes can be managed with interventions such as diet, exercise, and hypoglycemic medication. Ovarian cancer is a much rarer disease and is less amenable to prevention. It affects approximately 25,000 women/year in the United States. Given that it will take 7-10 years of yearly or more frequent screening of postmenopausal women to see a reduction in mortality, universal screening may not be a reasonable approach. The counter-argument is that ovarian cancer is a deadly and poorly understood disease.

Should we use our diminishing resources to screen all postmenopausal women for a rare disease, albeit a deadly one? Should we screen 200,000 to save 200 lives? There are approximately 40 million women older than 50 years of age in the United States, based on the 2014 census bureau data. To screen all of those women at $1,000/year would be conservatively $39.9 billion per year to find 15,942 cancers or approximately $2.5 million per cancer detected. In addition, approximately 398,571 women would undergo an unnecessary surgery. Assuming the cost of each unnecessary surgery was $10,000/person, the screening would result in an additional cost of almost $4 billion. Of those 15,942 cancers detected, this study suggests that without screening, 41% would survive five years, compared to 64% if they had been screened with the MMS approach. This would be a real number of 9,405 deaths instead of 5,739 deaths, a survival benefit for 3,666 women. The cost per patient who survived because of the MMS screening would be approximately $2.2 billion. This number sounds like a preposterous amount of money and may be overstated given estimates of the population > 50 years of age. Even if one assumes that only 50% of the population would be screened, this amount still would be an enormous cost for medical care to improve survival by 23% for a rare disease.

From the perspective of a screening test, focusing on women at higher risk than the general population would identify at least 25%, or more, of the cases of ovarian cancer and may allow intervention before cancer occurs by identifying these women and offering them prophylactic strategies. Using oral contraceptives for more than 10 years would reduce the incidence of ovarian cancer by more than 50% and may be a more reasonable approach for low-risk women when they are premenopausal. Spending an extra $1,000 (the cost of MMS screening) for screening over a woman's postmenopausal lifetime may not be worth considering, given that at least half of the population with diabetes are not being screened and, therefore, not diagnosed with a treatable disease that has high prevalence.

There have been significant questions about the role of screening for many diseases in terms of lead-time bias, cost, false-positive and false-negative tests, and whether screening actually saves lives. The cost always must be balanced against the potential benefit, and it isn't clear that we should choose universal screening for postmenopausal women in lieu of other more effective interventions.

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CE/CME QUESTIONS

1. **According to the latest data from the National Center for Health Statistics of the Centers for Disease Control and Prevention (Romero L, Pazol K, Warner L, et al. *MMWR Morb Mortal Wkly Rep* 2016; 65:409-414), the national teen birth rate has declined by what percentage since 2006?**

   A. 25%
   B. 32%
   C. 41%
   D. 53%

2. **The contraceptive implant Nexplanon relies on which drug for its effectiveness?**

   A. Etonogestrel
   B. Desogestrel
   C. Levonorgestrel
   D. Drospirenone

3. **What is the new direct oral anticoagulant?**

   A. Enoxaparin
   B. Rivaroxaban
   C. Warfarin
   D. Rifampin

4. **What is the current treatment for genitourinary syndrome of menopause?**

   A. Low-dose estrogen in the vagina through creams, pills, or rings
   B. Black cohosh
   C. St. John's wort
   D. Oral estrogen

CE/CME 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.