CONTRACEPTIVE TECHNOLOGY UPDATE®

THE TRUSTED SOURCE FOR CONTRACEPTIVE AND STI NEWS AND RESEARCH SINCE 1980

APRIL 2019 Vol. 40, No. 4; p. 37-48

INSIDE

Counseling on Contraceptive Use for Patients With Coexisting Medical Conditions

Focus on latest evidence to help patients make the most effective choices

For women with coexisting medical conditions, decisions regarding contraception are critical. Chronic medical conditions can cause maternal and fetal health complications during pregnancy, which can make pregnancies that are unintended or mistimed especially problematic.[1] A 2016 study indicated that among females ages 14-25 who received prescriptions for teratogenic medications, fewer than 30% also had contraceptive use documented.[2] In an analysis of a nationwide healthcare claims database of reproductive-age women who were enrolled in private insurance in 2004-2011, researchers found that, despite the potential for serious pregnancy-associated maternal and fetal risks, contraceptive use among women with medical conditions was not optimal.[3]

The American College of Obstetricians and Gynecologists (ACOG) recently has released a practice bulletin to help providers use scientific evidence in guiding affected patients to make the most effective choices.[4] The publication aims to help clinicians use the rating system offered in the *U.S. Medical Eligibility Criteria for Contraceptive Use* (*US MEC*), published by the Centers for Disease Control and Prevention.[5] The 2016 *US MEC* contains more than 1,800 recommendations for more than 60 conditions in clinical practice.

The *US MEC* is the leading resource in determining contraceptive eligibility, notes **Anita Nelson**, MD, professor and chair, Obstetrics and Gynecology, Western University of Health Sciences in Pomona, CA. The new bulletin provides more background information for readers, she explains.

"For example, the diagnostic criteria for migraine and migraine with aura headaches is useful," says Nelson. "Having a

Financial Disclosure: Consulting Editor **Robert A. Hatcher**, MD, MPH, Nurse Planner **Melanie Deal**, MS, WHNP-BC, FNP-BC, Author **Rebecca Bowers**, Column Author **Adam Sonfield**, Executive Editor **Shelly Morrow Mark**, Copy Editor **Josh Scalzetti**, and Editorial Group Manager **Terrey L. Hatcher** report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

CONTRACEPTIVE TECHNOLOGY UPDATE®

Contraceptive Technology Update® (ISSN 0274-726X), is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals Postage Paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to: *Contraceptive Technology Update*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

SUBSCRIBER INFORMATION:
Customer Service: (800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

SUBSCRIPTION PRICES:
Print: 1 year with free *AMA PRA Category 1 Credits*™: $479. Add $19.99 for shipping & handling. Canada: $509 per year plus GST. Elsewhere: $509 per year.
Online only: 1 year (Single user) with free *AMA PRA Category 1 Credits*™: $431.

MULTIPLE COPIES: Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at groups@reliasmedia.com or (866) 213-0844.

Back issues: $75. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
GST Registration Number: R128870672.

ACCREDITATION: Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [1.5] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Relias LLC designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This activity is intended for OB/GYNs, nurses, nurse practitioners, and other family planners. It is in effect for 36 months from the date of publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

AUTHOR: Rebecca Bowers
EXECUTIVE EDITOR: Shelly Morrow Mark
COPY EDITOR: Josh Scalzetti
EDITORIAL GROUP MANAGER: Terrey L. Hatcher
SENIOR ACCREDITATIONS OFFICER: Lee Landenberger

separate ACOG bulletin may popularize these recommendations."

The *US MEC* includes information about medical conditions and the use of contraceptive methods that are rated on a scale of 1 to 4 regarding safety. A category 1 designation indicates that there are no restrictions for using the contraceptive method, while a category 4 rating indicates that the method could present an unacceptable health risk for the patient. (*See the box for an explanation of the four categories.*)

Work Through the Options

Use of hormonal contraception in women with a history of venous thromboembolism (VTE) or at risk of a thromboembolic event is addressed in the new publication. Women with the following conditions associated with VTE should be counseled about nonhormonal or progestin-only contraceptives:

- Smoking and age 35 years or older;
- Less than 21 days after giving birth or 21-42 days after giving birth with other risk factors (such as age 35 years or older, previous VTE, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, body mass index of 30 or greater, postpartum hemorrhage, post-cesarean delivery, preeclampsia, or smoking);
- Major surgery with prolonged immobilization;
- History of deep vein thrombosis or pulmonary embolism;
- Hereditary thrombophilia (including anti-phospholipid syndrome);
- Inflammatory bowel disease with active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, or fluid depletion;
- Systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies;
- Superficial venous thrombosis (acute or history).[5]

The *US MEC* classifies the use of combined hormonal contraceptives in these women as category 3 (indicating that theoretical or proven risks usually outweigh the advantages of using the method) or category 4 (indicating that a condition represents an unacceptable health risk if the contraceptive method is used). Use of combined hormonal contraceptives is contraindicated in women with known familial thrombophilias, placing this condition in category 4.

How can clinicians counsel such patients in selecting appropriate contraceptive methods? Counseling for progestin-only or nonhormonal methods such as the copper intrauterine device (IUD) is similar to all contraceptive counseling, says **Rebecca Allen**, MD, MPH, associate professor of obstetrics and gynecology in the Warren Alpert Medical School of Brown University.

"It is important to elicit the patient's values and desires regarding a contraceptive method in terms of

What Are the Four *US MEC* Categories?

1 – A condition for which there is no restriction for the use of the contraceptive method
2 – A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
3 – A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
4 – A condition that represents an unacceptable health risk if the contraceptive method is used

Source: Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-103.

EXECUTIVE SUMMARY

The American College of Obstetricians and Gynecologists has released a practice bulletin to help providers use scientific evidence to guide women with coexisting medical conditions in making the most effective choices.

- The publication aims to help clinicians use the rating system offered in the *U.S. Medical Eligibility Criteria for Contraceptive Use* (*US MEC*). The 2016 *US MEC* contains more than 1,800 recommendations for more than 60 conditions in clinical practice.
- The guidance addresses topics such as use of hormonal contraception in women with a history of venous thromboembolism and contraceptive options for women of older reproductive age.

what matters most to the patient, for example, efficacy, bleeding profile, or ease of use, as well as inquiring about past contraceptive history and obtaining a full understanding of their current medical condition," says Allen, a co-author of the current bulletin. "Women who value having monthly withdrawal bleeds should be steered towards the copper IUD if all else is equal."

For progestin-only methods, the 52-mg dose levonorgestrel IUD can offer lighter or no withdrawal bleeding and treatment of heavy menstrual bleeding, which may be an issue if the patient is using anticoagulants, states Allen. The etonogestrel implant can cause unpredictable bleeding and spotting, but this spotting typically is light for most women. The progestin-only pill is effective with strict daily adherence, but also may cause irregular bleeding and spotting, she notes. Depot medroxyprogesterone acetate requires injections every three months, and ultimately can lead to high rates of amenorrhea with continued use. Barrier methods also are an option for motivated patients, states Allen.

Consider Options for Perimenopause

What are the contraceptive options for women of older reproductive age? There are no contraindications to the use of any hormonal contraceptives based on age alone, says **Andrew Kaunitz**, MD, associate chair of the Department of Obstetrics and Gynecology at the University of Florida College of Medicine-Jacksonville and medical director of the UF Health Women's Specialists – Emerson. That acknowledged, age is an important risk factor for many medical conditions, he notes.

For instance, among women of older reproductive age (above age 35), those who smoke, have hypertension, are significantly obese, or have migraine headaches with aura should avoid combination estrogen-progestin contraceptives (which the *US MEC* categorizes as 3-4 for these conditions), states Kaunitz. In contrast, healthy, nonsmoking women without specific risk factors for cardiovascular disease can safely continue combination hormonal contraceptives until ages 50-55.

"In my practice, women without contraindications to combination contraceptives and who continue to need contraception often choose to continue their method until age 55, when the likelihood of fecundability becomes very low," observes Kaunitz. "Although often performed, checking FSH levels is not useful in this clinical setting. Upon achieving age 55, some women in my practice choose to seamlessly transition from combination contraceptives to estrogen-progestin menopausal hormone therapy."

Perimenopausal women who are appropriate candidates can benefit not only from effective contraception provided by combination methods, but also from the positive effect on bone mineral density, prevention/treatment of abnormal uterine bleeding, suppressed vasomotor symptoms, and the reduced future risk of ovarian and endometrial cancer associated with using combined hormonal contraceptives, Kaunitz comments. The 52-mg levonorgestrel IUD, which can be used regardless of the presence of contraindications to combination hormonal contraceptives, is effective in managing abnormal uterine bleeding, which is common among women of older reproductive age, he states. ■

REFERENCES

1. Teal SB, Ginosar DM. Contraception for women with chronic medical conditions. *Obstet Gynecol Clin North Am* 2007;34:113-126.
2. Stancil SL, Miller M, Briggs H, et al. Contraceptive provision to adolescent females prescribed teratogenic medications. *Pediatrics* 2016;137:1-8.
3. Champaloux SW, Tepper NK, Curtis KM, et al. Contraceptive use among women with medical conditions in a nationwide privately insured population. *Obstet Gynecol* 2015;126:1151-1159.
4. [No authors listed]. ACOG Practice Bulletin No. 206: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol* 2019;133:e128-e150.
5. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-103.

Providers Can Improve Teen HPV Vaccination Rates

According to a new study, only about 16% of U.S. adolescents have received the complete vaccination against human papillomavirus (HPV) by the time they turn 13 years of age, despite national recommendations for vaccination at ages 11-12.[1]

Although HPV vaccination coverage has improved, providers still are falling behind when it comes to providing immunization at younger ages, says **Robert Bednarczyk**, PhD, assistant professor in the Hubert Department of Global Health and Department of Epidemiology at Emory University's Rollins School of Public Health. Clinicians need to improve their efforts in recommending the HPV vaccine during routine visits and adolescent and well-child visits, particularly focusing on children 11 to 12 years of age, notes Bednarczyk, who served as lead author of the study.

To perform the analysis, investigators looked at 2016 data from the National Immunization Survey-Teen (NIS-Teen), which monitors vaccination coverage among adolescents 13-17 years of age. Survey participants are the parents or guardians of teens in the selected age set, who provide information about their children's sociodemographic characteristics and vaccination providers.

According to the analysis, although 43.4% of teens ages 13-17 were completely vaccinated against HPV, just 15.8% of adolescents had received all of the recommended doses of the vaccine by their 13th birthday. About 34.8% of teens had received full vaccination by their 15th birthday.[1] Adolescent females were more likely than adolescent males to be up to date on the vaccine by the specified cutoff ages (20.1% vs. 11.6%, respectively, for vaccine completion before 13 years of age; 41.6% vs. 28.3%, respectively, for vaccine completion before 15 years of age).[1]

In a 2017 study conducted by the Centers for Disease Control and Prevention (CDC), which also looked at 2016 NIS-Teen data, researchers found that 43.4% of teens ages 13-17 were up to date with the recommended HPV vaccination series (49.5% for females; 37.5% for males).[2]

EXECUTIVE SUMMARY

According to a new study, only about 16% of U.S. adolescents have received the complete vaccination against human papillomavirus (HPV) by the time they turn 13 years of age, despite national recommendations for vaccination at ages 11-12.

- The analysis indicates that while about 43.4% of teens ages 13-17 received complete vaccination against HPV, just 15.8% of adolescents had received all recommended doses of the vaccine by their 13th birthday. Data show that about 34.8% of teens had received full vaccination by their 15th birthday.
- About 33,700 women and men are diagnosed every year in the United States with a cancer caused by HPV infection. Vaccination against HPV could prevent more than 90% of these cancer cases from ever developing, data indicate.

Early Vaccination Is Key

Why is it important that HPV vaccination begin so early? Public health officials say receiving the vaccine on time protects preteens long before they are ever exposed to the virus.

By not receiving the vaccine on time, more young Americans are at risk for cancers associated with HPV infection. The current national Healthy People 2020 goal for HPV vaccination in the United States is 80%. Data indicate that failure to reach that goal could result in more than 50,000 future cervical cancer cases for the current population of girls 12 years of age and younger.[3]

Much hinges on clinicians' recommendation practices when it comes to HPV vaccination.[4] Research indicates that most teens who receive a provider's recommendation for HPV vaccination receive the immunization.[5] However, not all providers are delivering the message. Reports from parents indicate that about half of eligible teens receive such vaccine recommendations.[5] About one-third of physicians recommend HPV vaccination for most of their patients who are 11-12 years of age.[6]

According to the CDC, 33,700 women and men are diagnosed every year in the United States with a cancer caused by HPV infection. The CDC estimates that HPV vaccination could prevent more than 90% of these cancer cases (31,200) from ever developing. In general, HPV is thought to be responsible for more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, and more than 60% of penile cancers. Tradition-

ally, oropharyngeal cancers have been caused by tobacco and alcohol use, but recent studies indicate that about 70% of oropharynx cancers may be linked to HPV.

Information from the CDC indicates that cancers of the back of the throat (oropharyngeal cancer) have surpassed cervical cancer as the most common type of cancer caused by HPV. Unlike cervical cancer in women, there are no recommended screening tests for the other types of cancers caused by HPV, so they may not be found until they cause health problems.[7]

Video May Aid in Effort

Just-published research indicates that patient-centered education strategies delivered in the provider's office could lead to more people choosing HPV vaccination.[8] The research was conducted by scientists from Regenstrief Institute, Indiana University School of Medicine and Indiana University Richard M. Fairbanks School of Public Health at Indiana University-Purdue University Indianapolis.

To conduct the study, the research team developed a video detailing the risks and benefits of the HPV vaccine. Parents of children who had not received the HPV vaccine or had not completed the vaccine series were shown the video while they waited in the examination room of a pediatric clinic during a routine visit. The researchers used electronic health records, as well as the state's immunization registry system, to identify patients eligible for the study. A total of 1,596 eligible adolescents ages 11-17 were included in the trial; one-third visited a clinic where the video was available. The analysis indicates that the proportion of adolescents in whom a change in vaccine status was observed was greater among those who attended an intervention clinic (64.8%) compared to those who visited the control clinic (50.1%; odds ratio, 1.82; 95% confidence interval [CI], 1.47-2.25; $P < 0.001$). Among adolescents whose parents watched the video, there was a three times greater odds of receiving a dose of the HPV vaccine (78.0%; odds ratio, 3.07; 95% CI, 1.47-6.42; $P = 0.003$).[8]

"These results are very promising for those concerned with public health," notes primary author **Brian Dixon**, PhD, director of public health informatics at Regenstrief and associate professor at Indiana University. "If we can educate patients/caregivers at the doctor's office, where they can take immediate action for their health, we can ensure more eligible patients receive the HPV vaccine, potentially saving lives as well as healthcare dollars spent on treating disease." ■

> "RESEARCH INDICATES THAT MOST TEENS WHO RECEIVE A PROVIDER'S RECOMMENDATION FOR HPV VACCINATION RECEIVE THE IMMUNIZATION."

REFERENCES

1. Bednarczyk RA, Ellingson MK, Omer SB. Human papillomavirus vaccination before 13 and 15 years of age: Analysis of National Immunization Survey Teen data. *J Infect Dis* January 2019; doi: 10.1093/infdis/jiy682. [Epub ahead of print].
2. Walker TY, Elam-Evans LD, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years — United States, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:874-882.
3. Chesson HW, Ekwueme DU, Saraiya M, et al. The estimated impact of human papillomavirus vaccine coverage on the lifetime cervical cancer burden among girls currently aged 12 years and younger in the United States. *Sex Transm Dis* 2014;41:656-659.
4. Gilkey MB, Moss JL, McRee A-L, Brewer NT. Do correlates of HPV vaccine initiation differ between adolescent boys and girls? *Vaccine* 2012;30:5928-5934.
5. Stokley S, Jeyarajah J, Yankey D, et al. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014 — United States. *MMWR Morb Mortal Wkly Rep* 2014;63:620-624.
6. Vadaparampil ST, Kahn JA, Salmon D, et al. Missed clinical opportunities: Provider recommendations for HPV vaccination for 11-12 year old girls are limited. *Vaccine* 2011;29:8634-8641.
7. Centers for Disease Control and Prevention. HPV Vaccine is Cancer Prevention for Boys, Too! Available at: https://bit.ly/2smftx8. Accessed Feb. 21, 2019.
8. Dixon BE, Zimet GD, Xiao S, et al. An educational intervention to improve HPV vaccination: A cluster randomized trial. *Pediatrics* 2019;143. doi: 10.1542/peds.2018-1457.

Researchers Investigate Microneedle Skin Patch Technology for Contraception Delivery

Researchers are studying microneedle skin patch technology for providing a long-acting contraceptive that can be self-administered by women. Scientists are working with researchers at the Georgia Institute of Technology and the University of Michigan to develop patches with microneedles that deliver a hormonal contraceptive. The patches under study use technology originally developed to administer vaccines.

In animal testing, researchers found that an experimental contraceptive patch using microneedles provided a contraceptive hormone at a therapeutic level for more than a month after one application to the skin.[1]

There is great interest in providing more long-acting contraceptive options, notes **Mark Prausnitz**, PhD, Regents Professor in the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology.

"Our goal is for women to be able to self-administer long-acting contraceptives with the microneedle patch that would be applied to the skin for five seconds just once a month," said Prausnitz, the study's corresponding author, in a press statement.

The microneedle patch delivery platform represents an exciting advancement in women's health, says **Gregory Kopf**, PhD director of R&D Contraceptive Technology Innovation at FHI 360.

"This self-administered long-acting contraceptive will afford women discreet and convenient control over their fertility, leading to a positive impact on public health by reducing both unwanted and unintended pregnancies," said Kopf in a press statement.

Technology Holds Promise

Delivery of the drug involves hundreds of microneedles attached to a patch that is roughly the size of a coin. Each needle is about one millimeter in length. The patch is applied briefly to the skin; shifting the patch to one side applies a force that breaks off the microneedles into the skin. The patch backing then can be discarded. The microscopic needles stay under the skin's surface, where the medication releases slowly over time.

Georgia Tech researchers, led by postdoctoral research scholar Wei Li, developed a technique that allows the microneedles to break off from the backing material. Tiny air bubbles molded into the tops of the microneedles create a weakness in the structure that allows the needles to release easily.

The microneedles are made from biodegradable polymers that are commonly used in resorbable sutures, notes **Steven Schwendeman**, PhD, Ara Paul Professor and chair of the Department of Pharmaceutical Sciences at the University of Michigan. Schwendeman is a collaborator on the current project.

"We select polymer materials to meet specific design objectives such as microneedle strength, biocompatibility, biodegradation and drug release time, and formulation stability," said Schwendeman in a press statement. "Our team then processes the polymer into microneedles by dissolving the polymer and drug in an organic solvent, molding the shape, and then drying off the solvent to create the microneedles."

Time to Test in Human Studies

In developing the contraceptive patch, researchers looked at previous work that involved microneedle patches designed for vaccine administration. The findings from a Phase I clinical trial of influenza vaccine that used dissolving microneedles indicated that the microneedle patches could be used to administer the vaccine safely.

EXECUTIVE SUMMARY

Researchers are studying microneedle skin patch technology for providing a long-acting contraceptive method that can be self-administered.

- Delivery of the drug involves hundreds of microneedles, each less than a millimeter in length, attached to a small patch about the size of a coin. The patch is applied briefly to the skin. Shifting the patch to one side causes the microneedles to break off into the skin; the patch backing then can be discarded. The microscopic needles stay under the skin's surface, where the medication releases slowly over time.
- Researchers plan to study the use of levonorgestrel as the contraceptive agent in the patch.

The microneedles are so small that they only enter the upper skin layers, and patients do not perceive them as painful, findings suggest.[2]

Scientists do not know yet how the contraceptive patches using microneedles will work in humans, Prausnitz notes. Since researchers plan to work with the contraceptive hormone levonorgestrel, they believe that the patch will offer effective contraception, says Prausnitz.

"We also expect that possible skin irritation at the site of patch application will be minimal, but these expectations need to be verified in clinical trials," he states.

The contraceptive patches that were tested on animal models contained 100 microneedles, but researchers believe larger patches will be needed to provide an adequate dose of levonorgestrel for humans. The researchers are interested in developing a patch for application once every six months. By creating a six-month patch, the number of healthcare interventions could be minimized, which is useful in countries where people have limited healthcare access. However, the amount of drug that can be incorporated into a microneedle patch is limited, says Prausnitz. ■

REFERENCES

1. Li W, Terry RN, Tang J, et al. Rapidly separable microneedle patch for the sustained release of a contraceptive. *Nat Biomed Eng* 2019; January 2019. doi: 10.1038/s41551-018-0337-4.
2. Rouphael NG, Paine M, Mosley R, et al; TIV-MNP 2015 Study Group. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet* 2017;390: 649-658.

FDA Approves New Test for *Mycoplasma genitalium*

The Food and Drug Administration (FDA) has approved the first test to help with the diagnosis of *Mycoplasma genitalium*, a sexually transmitted infection (STI). The infection is associated with nongonococcal urethritis in men, as well as cervicitis and pelvic inflammatory disease in women. In 2015, the Centers for Disease Control and Prevention (CDC) listed *M. genitalium* as a public health threat.

Research findings indicate that the ribosomal ribonucleic acid-based *M. genitalium* assay demonstrated greater sensitivity than lab-developed or CE-marked DNA-based tests.[1,2] The test can be performed using urine, urethral, penile meatal, endocervical, or vaginal swab samples.

In the past, *M. genitalium* has been difficult to diagnose, says **Scott Gottlieb**, MD, FDA commissioner. With more reliable detection of the infection, providers may be able to tailor treatment better and use medications that are most likely to be effective, he notes.

"In cases where *M. genitalium* is detected, doctors can consider forgoing use of antibiotics that are known to be ineffective against *M. genitalium* and choose a treatment more likely to be appropriate," said Gottlieb in a press statement. "Having accurate and reliable tests to identify the specific bacteria that's causing an infection can assist doctors in choosing the right treatment for the right infection, which can reduce overuse of antibiotics and help in the fight against antimicrobial resistance."

EXECUTIVE SUMMARY

The Food and Drug Administration has approved the first test to help with the diagnosis of *Mycoplasma genitalium*, a sexually transmitted infection.

- In 2015, the infection was listed as a public health threat by the Centers for Disease Control and Prevention.
- *Mycoplasma genitalium* causes urethritis in men and is associated with cervicitis, pelvic inflammatory disease, preterm birth, and spontaneous abortion in women.

Understand the Infection

First identified in 1980, *M. genitalium* is a bacterium that can infect the reproductive tract and is transmitted through sexual contact. Unlike most other bacteria, it is difficult to grow in culture, taking about six months to develop. Researchers were hampered in studying the epidemiology of *M. genitalium* infections until polymerase chain reaction tests were developed in the early 1990s. The bacteria's genetic makeup leads to the development of antibiotic resistance; resistance rates are high, making treatment a challenge.

"Although *M. genitalium* is typically more common than gonorrhea, there is very little public awareness of

this rising sexually transmitted infection, which can cause serious and potentially devastating health problems," said **Damon Getman**, PhD, senior principal research scientist and director of research at Hologic, in a press statement.

The STI causes urethritis in men and is associated with cervicitis, pelvic inflammatory disease, preterm birth, and spontaneous abortion in women. According to the CDC's 2015 guidelines, *M. genitalium* is responsible for approximately 15-20% of nongonococcal urethritis cases, 20-25% of nonchlamydial nongonococcal urethritis cases, and approximately 30% of cases of persistent or recurrent urethritis.[3] In most settings, *M. genitalium* is more common than *N. gonorrhoeae* but less common than *C. trachomatis*.

Research indicates that a single 1-gram dose of azithromycin is significantly more effective than doxycycline against *M. genitalium*.[3] However, resistance to azithromycin is increasing; the median cure rate for men and women is approximately 85%, but it was only 40% in the most recent trial.[4] Cure rates for moxifloxacin range from 70-100%. Fluoroquinolones other than moxifloxacin are not recommended for the treatment of *M. genitalium*, according to the CDC. Recent research indicates treatment failure rates after treatment with azithromycin have increased because of the emergence of worldwide macrolide antimicrobial resistance in *M. genitalium*.[5]

Symptoms May Not Be Present

Detecting the presence of infection can be a challenge; about 40-75% of women and 70% of men are asymptomatic.[6] Women may present with increased or altered vaginal discharge; urethritis that is acute, persistent, and recurrent; dysuria or urgency; occasional intermenstrual bleeding or post-coital bleeding; cervicitis; or lower abdominal pain. Men may have such symptoms as urethritis, dysuria, urethral discharge, and proctitis.[6]

Additional research is needed to identify new antibiotic targets, determine potential vaccine targets, and understand the lifecycle of *M. genitalium* in reproductive tract tissues.[7] ■

REFERENCES

1. Unemo M, Salado-Rasmussen K, Hansen M, et al. Clinical and analytical evaluation of the new Aptima *Mycoplasma genitalium* assay, with data on *M. genitalium* prevalence and antimicrobial resistance in *M. genitalium* in Denmark, Norway and Sweden in 2016. *Clin Microbiol Infect* 2018;24:533-539.
2. Le Roy C, Pereyre S, Henin N, Bebear C. French prospective clinical evaluation of the Aptima *Mycoplasma genitalium* CE-IVD assay and macrolide resistance detection using three distinct assays. *J Clin Microbiol* 2017;55:3194-3200.
3. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64:1-137.
4. Manhart LE, Gillespie CW, Lowens MS, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: A randomized controlled trial. *Clin Infect Dis* 2013;56:934-942.
5. Murray GL, Bradshaw CS, Bissessor M, et al. Increasing macrolide and fluoroquinolone resistance in *Mycoplasma genitalium*. *Emerg Infect Dis* 2017;23:809-812.
6. Sethi S, Zaman K, Jain N. *Mycoplasma genitalium* infections: Current treatment options and resistance issues. *Infect Drug Resist* 2017;10:283-292.
7. Martin DH, Manhart LE, Workowski KA. *Mycoplasma genitalium* from basic science to public health: Summary of the results from a National Institute of Allergy and Infectious Diseases technical consultation and consensus recommendations for future research priorities. *J Infect Dis* 2017;216(suppl_2):S427-S430.

Trial Underway for Vaginal Ring Device Designed for HIV Prevention

Researchers are evaluating a vaginal ring designed to protect women against both HIV and herpes simplex virus type 2 (HSV-2) in a Phase I study. The trial is being conducted by researchers from the National Institutes of Health-funded Microbicide Trials Network (MTN) at three U.S. sites in Alabama, California, and Pennsylvania.

Each flexible polymer ring contains 1.4 g of tenofovir, an anti-HIV drug. The ring is designed to release an approximate 10-mg daily dose. The trial will be analyzing the safety of three months of continuous use.

To conduct the MTN-038 study, scientists plan to enroll about 50 healthy, HIV-negative participants who will be assigned to using either the tenofovir vaginal ring or a placebo ring

EXECUTIVE SUMMARY

Researchers are evaluating a vaginal ring designed to protect women against both HIV and herpes simplex virus type 2 in a Phase I study. The trial is being conducted by researchers from the National Institutes of Health-funded Microbicide Trials Network at three U.S. sites in Alabama, California, and Pennsylvania.

- Each flexible polymer ring contains 1.4 g of tenofovir, an anti-HIV drug. The ring is designed to release an approximate 10-mg daily dose. The trial will be analyzing the safety of three months of continuous use.
- Researchers hope the tenofovir ring will be acceptable for use for HIV prevention. While a similar tenofovir gel product was found to be safe, not all women were receptive to using it.

for 90 consecutive days, including during menstrual periods. Investigators will conduct medical and laboratory tests to determine the safety of the ring. Participants will be questioned about ring use, what they liked or disliked about it, and whether ring use interfered with sex. Results are projected to be available sometime in mid-2020.

Arlington, VA-based research group CONRAD is providing both the active tenofovir ring and placebo ring products for the study, as well as providing advisory information for the trial. Funding supporters include the U.S. Agency for International Development/U.S. President's Emergency Plan for AIDS Relief.

"In order to increase uptake and adherence, women need combination HIV/HSV prevention products that fit into their lifestyles," says **Gustavo Doncel**, MD, PhD, CONRAD's scientific and executive director. "We believe the 90-day tenofovir vaginal ring formulation will be much easier and more convenient to use than its vaginal gel counterpart, and hope that through continued clinical development, it becomes a new effective and safe option for women."

The International Partnership for Microbicides is seeking U.S. and global regulatory approval of a 25-mg dapivirine vaginal ring. If it is approved, the monthly dapivirine ring would be the first biomedical HIV prevention method developed specifically for women. (Contraceptive Technology Update *reported on the dapivirine ring; see the January 2019 article, "Researchers Release Initial Results on Developmental Vaginal Ring," https://bit.ly/2RXzuGs.*)

Moving Science Forward

The MTN-038 trial is one of two studies evaluating 90-day use of the tenofovir ring. Earlier studies looked at rings worn by women for an average of 15 days. No safety concerns were observed during these initial studies, with results indicating the ring could deliver enough of the drug to be protective against both HIV and HSV-2.[1]

CONRAD developed the 90-day tenofovir ring in collaboration with the University of Utah and Northwestern University. It also developed a combination tenofovir/levonorgestrel ring designed to protect against unintended pregnancy, HIV, and HSV. Both products are being evaluated by CONRAD and partners, including the Centers for Disease Control and Prevention, in an expanded safety and acceptability study based in Kenya. CONRAD holds a license from Gilead Sciences Inc. to develop tenofovir-based products for women.

Evaluating Tenofovir's Promise

Researchers hope the tenofovir ring will be acceptable for use for HIV prevention. A vaginal gel, also developed by CONRAD, underwent extensive testing, with large-scale trials conducted in Africa. Although the gel product was found to be safe, not all women were receptive to using it.[2]

No product can be effective if it is not used consistently, which was a challenge for women in previous studies, says MTN Principal Investigator **Sharon Hillier**, PhD, professor and vice chair of the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Pittsburgh School of Medicine and Magee-Womens Research Institute.

"Women need a range of options that will work within the context of their lives — products that they can and are willing to use," said Hillier in a press statement. "Many women, we have learned, say that a longer-acting product, like a vaginal ring, would be an attractive option."

Scientists are looking forward to further testing the ability of tenofovir to protect against HSV-2. Such preventive action was detected during testing of vaginal gel in HIV prevention trials.

"A product that offers protection against both HIV and HSV-2 could have an important public health impact, but first we need to establish that the tenofovir vaginal ring is safe and acceptable when used for 90 days," says **Albert Liu**, MD, MTN-038 protocol chair and study director of clinical research at the Bridge HIV Clinical Research Site, San Francisco Department of Public Health, one of the three sites conducting the study. "We hope to answer these and other key questions in the MTN-038 study

so that later-phase effectiveness studies might follow." ■

REFERENCES

1. Thurman AR, Schwartz JL, Brache V, et al. Randomized, placebo controlled phase I trial of safety, pharmacokinetics, pharmacodynamics and acceptability of tenofovir and tenofovir plus levonorgestrel vaginal rings in women. *PLoS One* 2018;13:e0199778.
2. Marrazzo JM, Ramjee G, Richardson BA, et al; VOICE Study Team. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015;372:509-518.

WASHINGTON WATCH

State Policymakers Work Toward and Against a Post-*Roe* Country

Adam Sonfield
Senior Policy Manager
Guttmacher Institute
Washington, DC

As of mid-February 2019, the federal government was grinding its gears slowly, with the executive branch still recovering after a record-long partial government shutdown and Congress scrambling to prevent another shutdown. Numerous attacks on sexual and reproductive health and rights were looming, including the expected imminent release of final regulations imposing a "domestic gag rule" on the Title X national family planning program.

Instead, for this month's column, we will focus on policymaking at the state level. In 2018, for the first time in recent memory, the number of enacted state policies promoting sexual and reproductive health and rights outpaced the number of new restrictions. According to an analysis by my Guttmacher Institute colleagues, 29 states and the District of Columbia enacted 80 measures in 2018 that expanded access to abortion, contraception, testing and treatment for sexually transmitted infections (STIs), reproductive healthcare for minors, infertility coverage, and comprehensive sex education.[1]

For example, six states and DC reinforced or expanded their requirements regarding insurance coverage of contraception. New Jersey and Utah sought federal permission to expand Medicaid eligibility for family planning services to individuals otherwise ineligible for the program. On the abortion front, Massachusetts repealed two long-standing abortion restrictions, and Washington state expanded insurance coverage for reproductive healthcare, including a requirement that plans cover abortion if they also cover maternity care.

By contrast, 15 states adopted 23 new restrictions on abortion and four restrictions on family planning providers in 2018. This constituted the fewest new abortion restrictions in at least a decade. New abortion restrictions included an Iowa law banning abortion at six weeks after the patient's last menstrual period (LMP), and laws in Louisiana and Mississippi banning abortion at 15 weeks after LMP. Because of court challenges, none of those laws are in effect.

Despite the overall trends for 2018, states have passed more than 400 abortion restrictions in just the past eight years. As of January 2019, 21 states can be considered hostile to abortion rights, while only four states can be considered supportive, according to a separate Guttmacher analysis that looked at six categories of restrictions and six categories of supportive policies.[2] Only four states had passed enough restrictions to be considered hostile by these standards in 2000.

Enter Justice Kavanaugh

With the appointment of Brett Kavanaugh to the U.S. Supreme Court in October 2018, state policymakers have turned their focus to *Roe v. Wade*. Even before then, in anticipation of a conservative shift in the Supreme Court, anti-abortion policymakers have been enacting measures clearly intended to challenge *Roe* by banning abortion at early stages in pregnancy or policing the reasons patients seek abortion care. Just one month after Justice Kavanaugh's appointment, voters in Alabama and West Virginia approved state constitutional amendments that could lead to outright bans on abortion if *Roe* is undermined or overturned.

Those attempts have continued in 2019, as new abortion restrictions cleared a legislative chamber in Kentucky, North Dakota, and Wyoming by the end of January.[3] And those challenges have continued in the courts as well: On Feb. 7, the Supreme Court narrowly put off a potential challenge to its abortion rights precedents. In a 5-4 decision, it temporarily blocked a Louisiana restriction that is nearly identical to one in Texas that the Court struck down in 2016.[4] If allowed to go into effect, that law could

have left the state with just a single abortion provider. That case, and many others on abortion, still may come before the Court for a full hearing later in 2019 or beyond.

Meanwhile, lawmakers supportive of abortion rights are looking for opportunities to protect and expand those rights. Potential approaches that states have explored in recent years include constitutional or statutory provisions affirming and protecting the basic right to abortion; laws expanding Medicaid and private insurance coverage of abortion; and policies to expand the pool of abortion providers, such as by allowing advanced practice clinicians to provide first-trimester abortion.[5]

Notably, on the anniversary of the *Roe* decision in January 2019, New York enacted its Reproductive Health Act, repealing its unconstitutional and unenforceable pre-*Roe* laws.[6] The new law codifies the right to abortion, as currently interpreted by the U.S. Supreme Court, allowing for abortion through fetal viability for any reason and allowing for abortion after fetal viability when the life or health of the woman is at risk. It also moves abortion out of the state's penal code and into its public health code, which will prevent women from being prosecuted for abortion, and it allows advanced practice clinicians to offer abortion care. Predictably, anti-abortion activists and policymakers, including President Trump, vilified the new law as promoting infanticide, highlighting the challenges facing those supportive of abortion rights.[7] ■

REFERENCES

1. Nash E, Gold RB, Ansari-Thomas Z, et al. State policy trends 2018: With Roe v. Wade in jeopardy, states continued to add new abortion restrictions. Guttmacher Institute, Dec. 11, 2018. Available at: https://bit.ly/2GKGTad. Accessed Feb. 20, 2019.
2. Guttmacher Institute. State abortion policy landscape: From hostile to supportive. Dec. 11, 2018. Available at: https://bit.ly/2TRGw1d. Accessed Feb. 20, 2019.
3. Guttmacher Institute. State policy updates: Major developments in sexual & reproductive health. Available at: https://bit.ly/2a5Qpq8. Accessed Feb. 20, 2019.
4. Liptak A. Supreme Court blocks Louisiana abortion law. *New York Times*, Feb. 7, 2019. Available at: https://nyti.ms/2Gg9ZPg. Accessed Feb. 20, 2019.
5. Nash E, Donovan MK. Ensuring access to abortion at the state level: Selected examples and lessons. *Guttmacher Pol Rev* 2019. Jan. 9, 2019. Available at: https://bit.ly/2SUSlmK. Accessed Feb. 20, 2019.
6. Furneaux R. It took nearly 50 years, but New York finally just decriminalized abortion. *Mother Jones* Jan. 23, 2019. Available at: https://bit.ly/2R8ca8J. Accessed Feb. 20, 2019.
7. Wang V. Trump, Pence lead G.O.P. seizure of late-term abortion as a potent 2020 issue. *New York Times*, Jan. 31, 2019. Available at: https://nyti.ms/2SYQFvS. Accessed Feb. 20, 2019.

COMING IN FUTURE MONTHS

- Researchers focus on new chlamydia treatment
- Evaluating effectiveness of prolonged device use
- Does obesity affect EC effectiveness?
- Focus on potential dimethandrolone undecanoate shot

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.

CME/CE INSTRUCTIONS

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 ReliasMedia.com and click on My Account to view your available CE activities. Tests are taken after each issue. First-time users must register on the site using the subscriber number 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 test, 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 emailed to you.

CME/CE QUESTIONS

1. **Use of combined hormonal contraceptives in women with known familial thrombophilias is classified as which category in the *US MEC*?**

   a. Category 1
   b. Category 2
   c. Category 3
   d. Category 4

2. **According to the Centers for Disease Control and Prevention, approximately how many women and men are diagnosed every year in the United States with a cancer caused by HPV infection?**

   a. Less than 20,000
   b. 25,500
   c. 33,700
   d. 42,600

3. **Which of the following is a symptom of *Mycoplasma genitalium*?**

   a. Change in bowel habits
   b. Anal fissure
   c. Dysuria or urgency
   d. Pronounced skin rash

4. **What is the antiretroviral drug in the vaginal ring developed by the International Partnership for Microbicides now seeking U.S. and global regulatory approval?**

   a. Dapivirine
   b. Zidovudine
   c. Stavudine
   d. Didanosine

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.