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## INSIDE





# Report: Hormonal Contraception Safer Than Expected for Women with Diabetes

*Study results expand pregnancy planning options for women who present with diabetes*

Strokes and heart attacks are rare for women suffering from diabetes who use hormonal contraception, with intrauterine devices (IUDs) and implants the safest options, according to a just-published analysis.[1]

This finding is important news for family planning providers and their patients. According to the CDC, 29.1 million people, or 9.3% of the U.S. population, suffer from diabetes. Of this number, 21 million are diagnosed, and 8.1 million are undiagnosed.[2] The incidence of diabetes among women of reproductive age (18-44 years) increased from 2.2 to 3.8 per 1,000 women between 1997 and 2013.[3] The prevalence of diabetes varies in different racial and ethnic groups, with American Indians and Alaskan Natives exhibiting the highest prevalence — more than twice that of non-Hispanic whites.[2]

"CLINICIANS NEED TO GET BEYOND THE IDEA THAT BIRTH CONTROL JUST MEANS 'THE PILL.' THERE ARE OPTIONS THAT ARE SAFE AND EFFECTIVE FOR ALL WOMEN, INCLUDING THOSE WITH DIABETES." ELEANOR BIMLA SCHWARZ, MD, MS, PROFESSOR OF INTERNAL MEDICINE AT UC DAVIS HEALTH SYSTEM

The study, one of the first to evaluate hormonal contraception and health outcomes in women presenting with a chronic condition, should encourage providers to include implants and IUDs in birth control discussions with diabetic patients.

"Clinicians need to get beyond the idea that birth control just means 'the Pill,'" says **Eleanor Bimla Schwarz**,




**Financial Disclosure:** Consulting Editor **Robert A. Hatcher**, MD, MPH, Nurse Planner **Melanie Deal**, MS, WHNP-BC, FNP-BC, Author **Rebecca Bowers**, Editor **Jonathan Springston**, Editor **Jill Drachenberg**, Executive Editor **Shelly Mark**, and Senior Accreditations Officer **Lee Landenberger** report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

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MD, MS, professor of internal medicine at UC Davis Health System and senior author of the study. "There are options that are safe and effective for all women, including those with diabetes."

## Review the Research

To conduct the study, researchers used 2002-2011 data from the Clinformatics Data Mart, a national health claims database that includes 15 million commercially insured people. The scientists identified women in the United States, ages 14-44 years, with an ICD-9-CM code for diabetes and a prescription for a diabetic medication or device. They examined contraceptive claims and compared time to thromboembolism (venous thrombosis, stroke, or myocardial infarction) among women with diabetes dispensed hormonal contraception, using a modification of Cox regression to control for age, smoking, obesity, hypertension, hyperlipidemia, diabetic complications, and history of cancer. The analysis excluded data for three months after women gave birth.[1]

The analysis identified 146,080 women with diabetes who experienced 3,012 thromboembolic events. Only 28% of reproductive-age women with diabetes submitted any claims for hormonal contraception, with the majority receiving estrogen-containing oral contraceptives. Further investigation indicated incidents of thromboembolism were highest among women who used the contraceptive patch (16 per 1,000 woman-years) and lowest among women who used IUDs (six per 1,000 woman-years) and subdermal implants (zero per 163 woman-years). Compared with use of intrauterine contraception, progestin-only injectable contraception was associated with increased risk of thromboembolism (12.5 per 1,000 woman-years; adjusted hazard ratio, 4.69; 95% confidence interval [CI], 2.51-8.77).[1]

"The absolute risk of thromboembolism among women with type 1 or 2 diabetes using hormonal contraception is low," researchers concluded. "Highly effective, intrauterine and subdermal contraceptives are excellent options for women with diabetes who hope to avoid the teratogenic effects of hyperglycemia by carefully planning their pregnancies."

The findings of this paper suggest that for women presenting with diabetes, implant and IUD contraception represent the safest birth control choices, while combination methods, as well as the contraceptive injection, represent choices associated with greater risk, notes **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.

"Given how prevalent diabetes has become among our reproductive-age patients, the findings of this study are important," Kaunitz says.

## What are Women with Diabetes Using?

Outcomes from this study indicate that the vast majority of women with diabetes (72%) did not receive prescription contraception of any kind, even though pregnancy planning is critical for this population. This finding is "alarming," since women suffering from diabetes become pregnant as often as other women, notes **Sarah O'Brien**, MD, lead author of the article and associate professor at The

Ohio State University.

"Pregnancy timing is critical for women with diabetes," O'Brien said in a release accompanying the study. "It's best to carefully plan pregnancies and ensure that the diabetes is under good control, because high sugars can cause an increased chance of birth defects."

Women are at high risk for diabetes if they are overweight (body mass index of 25 kg/m$^2$ or greater) and exhibit one or more of the following additional risk factors:

- low physical activity (less than 150 minutes of moderate-intensity activity, such as walking, per week);
- family history of type 2 diabetes;
- high-risk race/ethnicity (African American, American Indian or Alaska Native, Asian American, Hispanic or Latino, Native Hawaiian or Pacific Islander);
- have birthed a baby weighing nine pounds or more, or were diagnosed with gestational diabetes;
- high blood pressure (140/90 mmHg or higher);
- high cholesterol (240 mg/dL or higher); or
- history of polycystic ovarian syndrome.[4]

## Stress Importance of Planning

Women with diabetes who are planning for pregnancy should know that high blood sugar and teratogenic medications increase the risk of congenital anomalies. By planning their pregnancies, patients can achieve tight control, stop taking teratogens, stabilize comorbidities, and begin folate supplementation prior to conception. Multidisciplinary support will be needed to achieve tight control, with a goal of A1c levels of 7% prior to pregnancy, and 6% during pregnancy, if this can be achieved without hypoglycemia. Women with diabetes also are encouraged to take at least 600 mcg of folic acid per day. A baseline ophthalmology exam should be performed during the first trimester, with monitoring every trimester as indicated by degree of retinopathy.[5] *(Editor's Note: For more information, please see the webinar, "Managing Diabetes: Increasing Provider Understanding of Reproductive Health Implications" [http://bit.ly/1Ylz0K1], and click on the individual presentations.)*

For women who are not planning pregnancy, check the *U.S. Medical Eligibility Criteria for Contraceptive Use* (US MEC) for guidance.[6] Women with diabetes are eligible candidates for a contraceptive that contains estrogen; use of combination pills, the contraceptive patch, and the vaginal ring for women with a history of gestational diabetes are classified as Category 1 (no restrictions for use), while use in women with type 1 or type 2 diabetes with no evidence of vascular disease falls in Category 2, meaning the chosen method generally can be used, with follow-up as needed. For women with diabetes and complications (nephropathy, retinopathy, neuropathy, or other vascular disease) or diabetes of more than 20 years' duration, use of estrogen-containing methods falls in Category 3 (usually not recommended; clinical judgment and continuing access to clinical services are required for use) or Category 4 (should not be used), depending on the severity of the condition.[6] ■

## EXECUTIVE SUMMARY

Strokes and heart attacks are rare for women with diabetes who use hormonal contraception, with intrauterine devices and implants serving as the safest options, according to a just-published analysis.

- Highly effective, intrauterine and subdermal contraceptives are excellent options for women with diabetes who hope to avoid the teratogenic effects of hyperglycemia by carefully planning their pregnancies, the study's authors noted.
- For women 18-79 years of age, age-adjusted incidence of diagnosed diabetes has increased since the 1980s; in 1980, the age-adjusted incidence rate was 3.5, while in 2014, it was 6.5.

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# New CDC Report Emphasizes Importance of Zika Screening

A new CDC report shows that among pregnant women in the United States with completed pregnancies and laboratory evidence of possible recent Zika infection, 6% overall delivered a fetus or infant with evidence of a Zika-related birth defect, and among women with first-trimester Zika infection, 11% delivered a fetus or infant with a birth defect.[1]

The report combined data from the continental United States and Hawaii that were collected in collaboration between CDC and state and local health departments to monitor pregnancies with laboratory evidence of Zika virus infection. As of Sept. 22, 2016, 442 women with possible Zika virus infection in the U.S. Zika Pregnancy Registry had completed their pregnancies. Twenty-six of the completed pregnancies (6%) were reported to demonstrate one or more of the birth defects potentially related to Zika virus infection during pregnancy. Among women infected with Zika in the first trimester of pregnancy, 11% were reported to deliver fetuses or infants with birth defects.[1]

Research indicates that the proportion of pregnancies with birth defects was similar for pregnant women who did or did not experience symptoms, about 6% in each group. The 18 infants with a finding of microcephaly represent 4% of the completed pregnancies. Researchers note this prevalence is substantially higher than the background prevalence of microcephaly in the United States of about seven per 10,000 live births, or about 0.07% of live births.

Scientists note that the 26 birth defects occurred among fetuses/infants of pregnant women who were exposed to Zika virus during their pregnancies in the following locations with active Zika virus transmission: Barbados, Belize, Brazil, Colombia, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Republic of Marshall Islands, and Venezuela.

This study indicates that the rate of microcephaly and other fetal malformations related to Zika is similar among babies born in the United States — whose mothers were infected during travel to a dozen countries with active Zika transmission — to the estimated rate in Brazil, observes CDC Director **Tom Frieden**, MD, MPH.

"Zika poses a real risk throughout pregnancy, but especially in the first trimester; it's critical that pregnant women not travel to areas where Zika is spreading," Frieden said in an announcement accompanying the data publication.

The report highlights the importance of CDC guidance to test all pregnant women (http://bit.ly/2bRQag6) with possible exposure to Zika virus regardless of whether they exhibited symptoms of Zika, and to test infants (http://bit.ly/2j8aBrQ) born to mothers with possible Zika virus infection.

## Follow CDC Recommendations

The CDC continues to recommend that pregnant women not travel to areas with reported Zika outbreaks. If a pregnant woman travels to or lives in an area with active Zika virus transmission, she should discuss such travel with her healthcare provider and strictly follow steps to prevent mosquito bites and sexual transmission of Zika virus, including use of abstinence or condoms. *(For more information to offer patients, please visit: http://bit.ly/1shEBFh.)*

The CDC also continues encouraging women considering pregnancy and their partners in areas


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- The report highlights the importance of CDC guidance to test all pregnant women with possible exposure to Zika virus regardless of whether they exhibited symptoms of Zika, and to test infants born to mothers with possible Zika virus infection.
- The CDC continues recommending that pregnant women not travel to areas with Zika. If a pregnant woman travels to or lives in an area with active Zika virus transmission, she should discuss such travel with her healthcare provider and strictly follow steps to prevent mosquito bites and sexual transmission of Zika virus, including use of abstinence or condoms.

with active Zika transmission to talk to their healthcare providers about pregnancy planning so they know the risks and the ways to reduce them. *(For more information, please visit: http://bit.ly/2g4t2Ml.)*

Many of the short- and long-term effects of prenatal Zika infection on a baby are unknown. Until more is known, CDC advises following the *Interim Guidance for the Clinical Evaluation and Management of Infants with Congenital Zika Virus Infection — United States, August 2016*, for any baby diagnosed with congenital Zika virus infection.

## Winter Doesn't Deter Mosquito Activity

As temperatures fall this winter, public officials advise not to let guards down when it comes to mosquitoes that can carry the Zika virus. According to **James Diaz**, MD, DrPH, professor and program director of environmental/occupational health sciences at Louisiana State University Health New Orleans School of Public Health, not only can the eggs of *Aedes* species mosquitoes survive winter, wide variations in daytime temperatures can stimulate egg-laying and shorten the time it takes for mosquitoes to become infective after biting a person with Zika.

"What's more, researchers have shown that while relatively rare, *Aedes aegypti* mosquitoes are able to transmit Zika to their offspring, a mechanism allowing the virus to survive from one season to the next," Diaz said in a press statement accompanying the publication of his paper detailing the characteristics of the mosquitoes capable of transmitting the Zika virus in the United States.[2]

*Aedes* species eggs can survive in conditions that adult mosquitoes cannot, the paper notes. Even when their source of water has evaporated, these mosquito eggs can survive desiccation, remaining environmentally stable and viable up to a year — all it takes is a little rain for them to hatch, the paper states.[2]

"As we learn more about the consequences of Zika infection, including the recent revelation that babies of Zika-infected mothers who had normal head sizes at birth have been diagnosed with microcephaly months later, it is vital that we know this enemy and remain vigilant in protecting ourselves," Diaz concludes. ■

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# Group Calls for Folic Acid Supplementation to Prevent Neural Tube Defects

The U.S. Preventive Services Task Force (USPSTF) has just issued a recommendation that all women who are planning or capable of pregnancy take a daily supplement containing 0.4-0.8 mg (400-800 µg) of folic acid.[1] Why is folic acid supplementation so important?

Neural tube defects are major birth defects of the brain and spine that occur early in pregnancy due to improper closure of the embryonic neural tube, which may lead to a range of disabilities or death. Research indicates that daily folic acid supplementation in the periconceptional period can prevent neural tube defects, yet most women do not receive the recommended daily intake of folate from diet alone.[2,3]

Data collected from 2003-2006 indicate that three-quarters of nonpregnant women ages 15-44 do not consume the recommended daily intake of folic acid for preventing neural tube defects.[4] To update its 2009 recommendation, the USPSTF examined new evidence of the benefits and harms of folic acid supplementation in women of childbearing age.

"The task force found convincing evidence that the risk of neural tube defects can be reduced when women take a daily folic acid supplement of 400 to 800 micrograms," says USPSTF member **Alex Kemper**, MD, MPH, MS, professor of pediatrics at Duke University School of Medicine and associate division chief for research in the division of children's primary care at Duke University. "These supplements can be taken as a daily multivitamin, prenatal vitamin, or single tablet that has the recommended amount of folic acid."

## When Folic Acid is Most Critical

Taking folic acid before and during pregnancy can help protect babies

against neural tube defects; however, the critical period when folic acid supplements provide the most protective benefits begins one month before becoming pregnant and continues through the first three months of pregnancy.

"Since neural tube defects occur in the first few weeks of pregnancy, it is important for women to be taking the recommended amount of folic acid before they become pregnant," says **Laura Mitchell**, PhD, professor in the Department of Epidemiology, Human Genetics and Environmental Sciences, at The University of Texas Health Science Center at Houston. "Because approximately one-half of pregnancies in the United States are unplanned, the USPSTF recommendation holds for all reproductive-age women, whether or not they are planning a pregnancy, so that all pregnancies benefit from this preventive measure."

The FDA issued a mandate for folic acid fortification of grain products, such as enriched flour and bread, in January 1998. Even with fortification, nearly one-quarter of all reproductive-age women exhibit folate levels that are sub-optimal to prevent neural tube defects.[4] To help reduce the proportion of women with an inadequate intake of folic acid, the FDA in 2016 called for folic acid fortification of corn masa flour, which is used in foods such as tortillas, tacos, tortilla chips, and tamales. The addition of folic acid to corn masa flour specifically targets Hispanic women since they are at higher risk of neural tube defects than non-Hispanic women, tend to demonstrate lower blood folate levels, and consume fewer traditionally fortified foods. Despite food fortification, research indicates that women who do not take folic acid supplements are approximately three times more likely to exhibit sub-optimal folate levels compared to women who take supplements.[5]

"Even in the era of mandatory folic acid fortification of the food supply, taking a daily supplement remains a critical strategy for women to make sure they are receiving enough folic acid," says Mitchell, who wrote an editorial accompanying the USPSTF's recommendation.[6]

Women who present with a personal or family history of a pregnancy affected by a neural tube defect are at increased risk of experiencing a similar affected pregnancy. Some factors increase the risk of neural tube defects, including use of particular anti-seizure medications such as valproic acid or carbamazepine, maternal diabetes, obesity, and mutations in folate-related enzymes. These women may be advised to take higher doses of folic acid.[6] ■

## EXECUTIVE SUMMARY

The U.S. Preventive Services Task Force has issued a recommendation that all women who are planning or capable of pregnancy take a daily supplement containing 0.4-0.8 mg (400-800 µg) of folic acid.

- Research indicates that daily folic acid supplementation in the periconceptional period can prevent neural tube defects, yet most women do not receive the recommended daily intake of folate from diet alone.
- Taking folic acid before and during pregnancy can help protect babies against neural tube defects; however, the critical period when folic acid supplements provide the most protective benefits begins one month before becoming pregnant and continues through the first three months of pregnancy.

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# Task Force Recommends Against Genital Herpes Screening

Genital herpes is a common sexually transmitted infection (STI) in the United States for which there is no cure nor effective screening tests. The U.S. Preventive Services Task Force (USPSTF) has just published a final recommendation against using current blood tests to screen for genital herpes in patients with no signs or symptoms of infection, including adolescents and adults, as well as pregnant women.[1]

While genital herpes is common — the CDC estimates about one out of every six people ages 14-49 in the United States is infected — testing is not generally helpful for people without symptoms, in part because early identification does not improve a person's health, as there is no cure for the infection, says USPSTF member **Ann Kurth**, PhD, CNM, MSN, MPH, Dean and Linda Koch Lorimer Professor of Nursing at the Yale University School of Nursing.[2]

"In addition, because current screening methods are often inaccurate, harms of screening include high false-positive rates and potential anxiety and disruption of personal relationships related to diagnosis," Kurth noted in a statement accompanying the recommendation.

Genital herpes infection is caused by two subtypes of herpes simplex virus (HSV), HSV-1 and HSV-2. Unlike other infections for which screening is recommended, HSV infection may not demonstrate a long asymptomatic period during which screening, early identification, and treatment may alter its course. Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir.[3-6] Although these medications may provide symptomatic relief from outbreaks, they do not cure HSV infection. These systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy, but do not eradicate latent virus nor affect the risk, frequency, or severity of recurrences after discontinuing the drug.

To update its 2005 recommendation on screening, the USPSTF reviewed evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, including those who are pregnant, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others. The panel found that serologic screening for genital herpes is associated with a high rate of false-positive test results and potential psychosocial harms. Evidence from randomized, controlled trials does not establish whether preventive antiviral medication for asymptomatic HSV-2 infection has benefit, the panel concluded.[1]

"People who are concerned about their personal risk or are experiencing signs and symptoms of genital herpes should talk to their primary care clinician," says USPSTF member **Maureen Phipps**, MD, MPH, department chair and Chace-Joukowsky professor of obstetrics and gynecology and assistant dean for teaching and research on women's health at the Warren Alpert Medical School of Brown University. "This is especially true for women who are pregnant because clinicians can help women who have genital herpes minimize the chance of passing this on to their babies."

## New Drug in Research Focus

In related news, results of a small-scale, Phase II trial indicate a new medication may provide greater virus

### EXECUTIVE SUMMARY

The U.S. Preventive Services Task Force has published a final recommendation against using current blood tests to screen for genital herpes in people with no signs or symptoms of infection, including adolescents and adults, as well as pregnant women.

- Although genital herpes is common — the CDC estimates about one out of every six people ages 14-49 in the United States is infected — testing is not generally helpful for people without symptoms, in part because early identification does not improve a person's health, as there is no cure for the infection.
- Because of the inaccuracy of current screening methods, harms of screening include high false-positive rates and potential anxiety and disruption of personal relationships related to diagnosis.

suppression and reduction in lesions for patients with genital herpes.[7] In the study, researchers with the University of Washington and Fred Hutchinson Cancer Research Center compared the medications pritelivir and valacyclovir for reducing genital herpes simplex virus shedding and lesions in persons with recurrent genital herpes.

For the crossover study, 91 participants (adults with four to nine annual genital HSV-2 recurrences) were randomly assigned to two groups: 45 to receive pritelivir first, and 46 to receive valacyclovir first. Participants took the first drug for 28 days, followed by 28 days of washout before taking the second drug for 28 days. Throughout treatment, the participants collected genital swabs four times daily for HSV testing. The FDA placed the trial on clinical hold based on findings in a concurrent nonclinical toxicity study, and the sponsor terminated the study.

Of the 91 randomized participants, 56 had completed both treatment periods at the time of the study's termination. In intent-to-treat analyses, HSV shedding was detected in 2.4% of swabs during pritelivir treatment, compared with 5.3% during valacyclovir treatment. Genital lesions were present on 1.9% of days in the pritelivir group vs. 3.9% in the valacyclovir group. Researchers note the frequency of shedding episodes did not differ by group. Quantity of virus shed decreased significantly during pritelivir treatment compared with valacyclovir treatment. The frequency of pain was lower in the pritelivir group compared to the valacyclovir group. Treatment-emergent adverse events occurred in 62% of participants in the pritelivir group and 69% of participants in the valacyclovir group.[7]

Although clinical trials conducted so far in humans have shown no serious side effects, the FDA put a hold on the drug's clinical use in 2013 because of skin and blood abnormalities shown in a concurrent animal trial. The hold came while the University of Washington study was underway, forcing it to end early.

The German drug maker AiCuris is working with the FDA to partially lift the hold so that pritelivir can be tested in a new clinical trial on patients who are resistant to drugs in the acyclovir family, which includes acyclovir, famciclovir, and valacyclovir.

"I hope that if the trial for acyclovir-resistant HSV goes well, we would be able to go back to the general population with further trials," said lead author **Anna Wald**, MD, MPH, University of Washington and Fred Hutchinson Cancer Research Center researcher. "It's important to develop new drugs for this incredibly common infection." ■

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# Talk with Older Women About Sexual Activity

Although older women are sexually active beyond their seventh decade of life, results of a new study indicate that at least one in seven women ages 65-79 suffers from hypoactive sexual desire dysfunction (HSDD).[1] HSDD is characterized by low sexual desire that causes marked distress or interpersonal difficulty. The condition is not the result of a coexisting medical or psychiatric condition, problems within the

relationship, or the effects of a medication or other drug substance. Research indicates the condition is thought to affect one in 10 women.[2]

In the new data, designed as a questionnaire-based, cross-sectional study, more than 1,500 Australian women were assessed for sexual function and sexual distress as defined by the Female Sexual Function Index and the Female Sexual Distress Scale-Revised. The group consisted of 52.6% partnered women, with a mean age of 71 years. Within this group, 88% were found to experience low sexual desire, 15.5% experienced sexually related personal distress, and 13.6% exhibited HSDD, defined as the presence of both low sexual desire and sexually related personal distress. This percentage was higher than what had been reported previously for women in this age group and similar to the prevalence reported for younger women, researchers noted.

Although HSDD was found to be more common in women with partners, data indicate that unpartnered older women are sexually active and may be distressed by low sexual desire.[1] Independent factors included experiencing vaginal dryness during intercourse in the past month, experiencing moderate to severe depressive symptoms, and demonstrating symptomatic pelvic floor dysfunction.

"This study demonstrates that healthcare providers need to have honest and open discussions with their patients as they age with regard to desire, mood, vaginal dryness, and pelvic floor issues to determine whether these factors are affecting a woman's desire or ability to be sexual," says **JoAnn Pinkerton**, MD, NCMP, executive director of the Cleveland-based North American Menopause Society.

## EXECUTIVE SUMMARY

Although older women are sexually active beyond their seventh decade of life, results of a new study indicate that at least one in seven women ages 65-79 suffers from hypoactive sexual desire dysfunction.

- Hypoactive sexual desire disorder is characterized by low sexual desire that causes marked distress or interpersonal difficulty. The condition is not the result of a coexisting medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance.
- Healthcare providers must engage in honest and open discussions with their patients as they age regarding desire, mood, vaginal dryness, and pelvic floor issues to determine whether these factors are affecting a woman's desire or ability to be sexual.

## Searching for More Options

In 2015, the FDA approved flibanserin (Addyi), the first drug specifically indicated for hypoactive sexual desire dysfunction. *(*Contraceptive Technology Update *reported on the regulatory move in November 2015, "FDA approves first treatment for sexual desire disorder," available at: http://bit.ly/2irJaYh.)* Originally developed as an antidepressant, flibanserin works on three neurotransmitters: dopamine, norepinephrine, and serotonin. Flibanserin works by increasing levels of dopamine and norepinephrine, while dropping levels of serotonin. This drug interaction is intended to increase chemicals that help promote sexual desire and decrease the one that can suppress desire.

Addyi comes with a boxed warning to highlight the risks of severe hypotension and syncope in patients who drink alcohol during treatment with the drug, in those who also use moderate or strong CYP3A4 inhibitors, and in those who suffer from liver impairment. The drug is contraindicated in these patients. In addition, the FDA requires that three studies in women be conducted to better understand the known serious risks of the interaction between Addyi and alcohol.

Patients using flibanserin should take the drug, dosed as a 100 mg tablet, at bedtime to help decrease the risk of adverse events occurring due to possible hypotension, syncope, and central nervous system depression, such as sleepiness and sedation. Women should discontinue treatment after eight weeks if they do not report an improvement in sexual desire and associated distress. The most common adverse reactions associated with drug use are dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth. Clinicians must be trained and certified to prescribe Addyi. *(For more information, please visit: http://bit.ly/2knu6QC.)*

A 2016 overview of clinical evidence on use of the drug concludes that treatment with flibanserin, on average, resulted in one-half additional satisfying sexual event (SSE) per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue.[3]

The analysis is based on five published and three unpublished studies including 5,914 women. Women's mean global impression of improvement scores indicated minimal improvement to no change, the analysis noted.

Overall, the quality of the evidence

was graded as very low, the article concluded. Before the drug can be recommended in guidelines and clinical practice, future studies should include women from diverse populations, particularly women with comorbidities, medication use, and surgical menopause, it stated.[1]

Scientists are studying the possible use of bremelanotide as a subcutaneous, on-demand, as-needed treatment for premenopausal women diagnosed with HSDD. Bremelanotide, which is a melanocortin 4 receptor agonist drug candidate, is a synthetic peptide analog of the naturally occurring hormone alpha-MSH (melanocyte-stimulating hormone). It is under development by Palatin Technologies, Inc. The company announced in November 2016 favorable top-line results from the Reconnect Studies, its Phase III clinical trial program of bremelanotide.

The Reconnect Studies consist of two randomized, double-blinded, placebo-controlled studies comparing the efficacy and safety of bremelanotide vs. placebo in premenopausal women diagnosed with HSDD. The Reconnect Studies randomized 1,267 women with HSDD. The primary efficacy analysis population was the modified intent-to-treat patient population, consisting of 1,202 women presenting with HSDD in the United States and Canada. Patients self-administered either 1.75 mg of bremelanotide or placebo as needed in anticipation of sexual activity. The double-blind or efficacy portion of each study consisted of a 24-week treatment evaluation period. The open-label safety extension portion of the Reconnect Studies is ongoing. Publication of the data is forthcoming.

Hypoactive sexual desire disorder is the most prevalent form of female sexual dysfunction, says **Sheryl Kingsberg**, PhD, professor of reproductive biology at Case Western Reserve University School of Medicine and division chief, OB/GYN Behavioral Medicine, at University Hospitals Cleveland Medical Center. Data indicated "significant" reduction in distress with use of bremelanotide, noted Kingsberg, who was an investigator in the clinical trial. ■

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# New Injectable Focus of HIV PrEP Clinical Trial

The first large-scale clinical trial of a long-acting injectable drug for HIV prevention has just been launched. The Phase III study, which will enroll participants at 45 sites in Argentina, Brazil, India, Peru, South Africa, Thailand, the United States, and Vietnam, will examine whether a long-acting form of the anti-HIV drug, cabotegravir, injected once every eight weeks, can safely protect people from HIV infection at least as well as a combination of anti-HIV medications taken daily as an oral tablet. Truvada, which consists of the anti-HIV drugs emtricitabine and tenofovir disoproxil fumarate, is the only medication currently approved for HIV pre-exposure prophylaxis (PrEP).

The HIV Prevention Trials Network has launched the HPTN 083 study to evaluate whether injectable cabotegravir can safely protect men who have sex with men and transgender women who have sex with men from acquiring HIV as well as daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).


## EXECUTIVE SUMMARY

A Phase III study will determine whether a long-acting form of the anti-HIV drug, cabotegravir, injected once every eight weeks, can safely protect people from HIV infection at least as well as Truvada, a combination of anti-HIV medications taken daily as an oral tablet.

- If found to be safe and effective for HIV pre-exposure prophylaxis, injectable cabotegravir may be easier for some people to adhere to than daily oral Truvada.
- The study will enroll 4,500 men who have sex with men and transgender women who have sex with men, all 18 years or older and at high risk for HIV infection, at 45 clinical sites.

If found to be safe and effective for HIV PrEP, injectable cabotegravir may be easier for some people to adhere to than daily oral TDF/FTC.

The study's creators will enroll 4,500 men who have sex with men and transgender women who have sex with men, all 18 years or older and at high risk for HIV infection, at 45 clinical sites. Results are expected in 2021.

The annual number of new HIV infections among young people, especially young men who have sex with men and transgender women who have sex with men, has been on the rise despite nearly flat HIV incidence among adults worldwide, noted **Raphael Landovitz**, MD, MSc, HPTN 083 protocol chair, in a statement regarding the trial enrollment.

"It is essential to develop multiple effective HIV prevention modalities so the most vulnerable populations have a choice of preventive options," said Landovitz, who serves as an associate professor of medicine at the David Geffen School of Medicine at UCLA, and associate director of the UCLA Center for Clinical AIDS Research & Education. "We hope injectable cabotegravir will become one such modality."

Researchers will follow participants in the HPTN 083 study for an average of 4.5 years. During their first five weeks after enrollment, study participants will receive two daily oral tablets: either cabotegravir or Truvada, and a placebo pill. Beginning in the sixth week, participants in the cabotegravir group will receive injections of cabotegravir and placebo tablets to be taken orally daily, while participants in the Truvada group will receive placebo injections and daily oral doses of Truvada tablets. Study staff will administer injections. The first two injections will occur four weeks apart, then once every eight weeks for an average of nearly 3.5 years. After completing the injections, all participants will be offered 48 weeks of PrEP with daily oral Truvada.

All study participants will receive HIV prevention counseling, condoms and lubricant, as well as counseling to encourage and support adherence to the daily oral pill. Participants will be tested for sexually transmitted infections (STIs) throughout the study and referred for appropriate treatment if diagnosed with an STI. Study participants who become HIV-infected during the trial will stop receiving the study products and be referred to local medical providers for HIV care and treatment.

"The HPTN 083 study has the potential to provide game-changing data as the first large-scale test of a long-acting injectable drug for HIV prevention," noted Protocol Co-Chair **Beatriz Grinsztejn**, MD, PhD, in the enrollment announcement. Grinsztejn directs the Instituto de Pesquisa Clinica Evandro Chagas HIV/AIDS Clinical Research Centre of the Oswaldo Cruz Foundation–Fiocruz in Rio de Janeiro, Brazil.

## Separate Study for Use in Women

Injectable cabotegravir also will be tested for HIV prevention in women. The HPTN 084 study will examine the safety and efficacy of injectable cabotegravir in a study that will take place in sub-Saharan Africa. The trial is expected to launch in 2017.

The National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health, is sponsoring HPTN 083. The funding for the HIV prevention research uses a new approach: NIAID is co-funding the trial with the pharmaceutical company ViiV Healthcare, while the NIH-funded HIV Prevention Trials Network is conducting the study. Both ViiV Healthcare and Gilead Sciences, Inc., are providing the study medications.

More HIV prevention tools are needed that fit easily into people's lives, says **Anthony Fauci**, MD, NIAID director. Taking a daily pill can be difficult for some people, so some individuals may find an every-eight-weeks dosage schedule more convenient. If injectable cabotegravir is found to be effective for PrEP, it may be an easier medication for some people to adhere to than a daily oral pill. Some people also may find periodic injections to be a more discreet form of HIV prevention than daily pills and, thus, may prefer injectable cabotegravir for that reason, public health officials note.

"Although daily oral Truvada clearly works for HIV prevention, taking a daily pill while feeling healthy can be difficult for some people," Fauci said in a statement. "If proven effective, injectable cabotegravir has the potential to become an acceptable, discreet, and convenient alternative for HIV prevention." ■

## COMING IN FUTURE MONTHS

- Genes may play role in more severe forms of PMS
- Help young men overcome barriers to reproductive health
- Research eyes vaginal bacteria's role in women's HIV susceptibility
- Contraception and sickle cell disease: What you should know

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# CME/CE QUESTIONS

1. **With regard to combination pills, the contraceptive patch, and the vaginal ring, what is the risk category for women with type 1 or type 2 diabetes with no evidence of vascular disease, according to the *US Medical Eligibility Criteria for Contraceptive Use*?**

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

2. **What are the current recommendations from the CDC regarding testing for the Zika virus?**

   a. All pregnant women with possible exposure to Zika virus should be tested, regardless of whether they demonstrate symptoms of Zika.
   b. Only pregnant women who have traveled to an area with active Zika infection or are with a partner who has traveled to a similar location should be tested.
   c. Only pregnant women who are with a partner who has tested positive for Zika infection should be tested.
   d. No current recommendations for testing are active at this time for women in the United States.

3. **What is the current U.S. Preventive Services Task Force recommendation for daily folic acid supplementation for all women who are planning or capable of pregnancy?**

   a. 0.2 to 0.4 mg
   b. 0.3 to 0.6 mg
   c. 0.3 to 0.7 mg
   d. 0.4 to 0.8 mg

4. **What is the current U.S. Preventive Services Task Force recommendation regarding screening for genital herpes using current blood tests?**

   a. Test only pregnant women prior to delivery.
   b. Test only those who plan to become pregnant.
   c. Test all sexually active persons.
   d. Do not use current blood tests to screen for genital herpes in people without signs or symptoms of infection.