



# CONTRACEPTIVE TECHNOLOGY UPDATE®

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## New Male Contraceptives May Be on the Horizon

*A decade away could be reality*

**T**he persistent joke among male contraceptive researchers is that a male contraceptive has been 10 years away for the last 50 years.

There have been exciting leads and thudding dead-ends since the 1970s. But contraceptive researchers and experts tell *Contraceptive Technology Update* that the end goal may finally be in sight.

“This is the analogy of eating an elephant one bite at a time,” says **Logan Nickels**, PhD, research director with Male Contraceptive Initiative in Durham, NC. “A core group of people have been working on this one for decades. Multiple candidates come to surface, and we’re hopeful we’ll see

multiple products come to the market with diverse characteristics.”

The groundwork is ready for a hormonal contraceptive

method to emerge over the next decade.<sup>1</sup> “Some of the data look good,” says **Daniel S. Johnston**, PhD, chief of the Contraception Research Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, MD.

The big question is whether researchers

will find an adequately safe method. “I’m confident they’ll get efficacy,” Johnston says. “I’m optimistic. I think we have spent a lot of time working on hormonal contraceptives.” He also is

**“THIS IS AN IMPORTANT SOCIAL ISSUE BECAUSE THERE ARE WOMEN YOU CAN’T JUST GIVE AN EFFECTIVE CONTRACEPTIVE TO, AND THEY DON’T WANT TO GET PREGNANT.”**



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hopeful there will be nonhormonal methods within two decades.

The male contraceptive technology field is much more enticing today than it was a decade ago, says **Anita L. Nelson, MD**, professor and chair of obstetrics and gynecology at Western University of Health Sciences in Pomona, CA. Some exciting progress has occurred in Phase II trials, but some obstacles remain.

“I wouldn’t be surprised if something happened, but also wouldn’t be surprised with slow progress,” Nelson adds.

## Administration, Funding Are Issues

The main difficulty of developing a male contraceptive is the challenge of finding the right administration, says **Brian T. Nguyen, MD, MSc**, assistant program director in the section of family planning and assistant professor in the department of obstetrics and gynecology at Keck School of Medicine at the University of Southern California.

Funding also is a major issue. Most research into male contraceptives comes from federal funding.

“No pharmaceutical company is funding production of these drugs,” he says.

The problem related to funding is that it has been episodic. “It will get moving in a direction, and then get cut off,” Nelson laments. “This is an important social issue because there are women you can’t just give an effective contraceptive to, and they don’t want to get pregnant.”

The Male Contraceptive Initiative has been granted more than \$3 million for nonhormonal male contraceptive research since receiving its first grant in 2017, says **Heather Vahdat, MPH**, executive director.

“The contraceptive space is a small space, and the number of people funding in the space is limited,” Vahdat says.

The total funding for male, nonhormonal, reversible contraception research and development was \$3.2 million in 2018. The Male Contraceptive Initiative was a main funder, along with the National Institutes of Health (NIH). The organization funds fellowships, seed grants, and vas occlusion research grants. (*More information is available at: <https://bit.ly/3iZS8M0>.*)

## EXECUTIVE SUMMARY

Researchers across the world are studying hormonal and nonhormonal male contraceptive products in hopes of being the first to bring a new, reversible contraceptive for men to market within the next 10 to 20 years.

- Funding and finding the right administration are two of the biggest challenges in bringing a male contraceptive to market.
- The Male Contraceptive Initiative in Durham, NC, is a major funder of nonhormonal male contraceptive research, providing around \$3 million in grants since 2017.
- Societal changes regarding gender dynamics and male participation in family planning have contributed to changes in how people think about gender responsibility, which makes a male contraceptive a more appealing prospect than it was several decades ago.

“We are a small fish,” Nickels says. “We’re doing everything we can in terms of an advocacy angle to increase awareness and bring male contraceptives to the forefront of the conversation. The time is right.”

## Gender Dynamics Are Changing

Massive societal changes in terms of gender dynamics and male participation in family planning have contributed to changes in how people think of gender responsibility. “People are finally asking the questions of ‘Why is that?’ and ‘Why has it always been that way?’” Nickels explains. “Men want to help their partners in family planning, or they might think, ‘I’m an autonomous man, and I’m not finding the options out there to fit my needs.’”

Men are limited to just two contraceptive options, neither of which is as convenient as a pill, patch, or injection: Condoms or vasectomy. Other than those, they could use the withdrawal method. “Men want something like an IUD for men, which is effective, but reversible,” Nelson explains.

“My hypothesis is there needs to be a huge culture change where men are demanding it and wanting to take it,” Nguyen adds.

Men have control over much of the pharmaceutical company leadership. Until they recognize their role in preventing unplanned pregnancy, they will prioritize women taking drugs and implants before they focus on men, Nguyen explains.

Men absolutely would like some control over contraception, says **Susan Wysocki**, WHNP, FAANP, medical director for the Partnership for Male Youths (PMY) in Washington, DC, a not-for-profit

organization that focuses on medical issues for males.

“What I hear from guys is ‘What if I don’t know that my partner has been inconsistent with contraception?’” Wysocki says. “Pregnancy potentially throws a wrench in their own personal plans. Men want to have a method that works for them, and that they have some control over potentially becoming a father.” Women also would welcome male contraception so they can ask their male partners to take turns with the responsibility of preventing pregnancy, Wysocki adds.

“We’re not providing an effective range of options for half the population of the world,” Vahdat says. “It’s frustrating to think that one of the challenges is the chicken and the egg [conundrum]. You’ve got people who want to demonstrate the demand, but you can’t do that with the existing products, and anything else you are doing is speculative work.”

Scientists working in the male contraceptive field have endured decades of disappointments. “I hope the [current male contraceptive projects] are successful, and we’re not far from a male contraceptive. We’ve been there before, and they tend to fail at the late stage,” Johnston says.

Over the years, researchers and clinicians have dramatically reduced hormones in the female contraceptive pill. They also created contraceptive rings and patches, Johnston notes.

“But with men, we haven’t found that window between where something is effective and where it is safe,” he adds. “The first goal is safety, and we have to have both safety and efficacy. A lot of male products fail because if they’re safe, they’re not effective — or if they’re effective, they’re not safe.”

After 40 years of research and more than 30 clinical trials, there

hopefully will be a breakthrough in male contraceptive research, Johnston says.

Nearly two decades into their research involving the male reproductive tract, a pair of researchers from Weill Cornell Medicine in New York City had an epiphany moment. “The enzyme we worked on was known to make sperm inactive if inhibited in a certain way,” says **Lonny Levin**, PhD. “We’ve known that for 17 years.”

Initially, the researchers were developing inhibitors for this enzyme — but not for contraception, says **Jochen Buck**, MD, PhD, professor at Weill Cornell.

When they injected the inhibitor into a male mouse, sperm could not be activated for six hours. The next day, the sperm were normal again, Buck explains.

“Essentially, 30 minutes after it’s given, sperm doesn’t work anymore,” he adds. “The next day, it’s working again.”

They developed the inhibitors as research tools, Levin says. (*See story about a possible new, nonhormonal contraceptive in this issue.*)

**Robert A. Hatcher**, MD, chairman of the *Contraceptive Technology Update* editorial board, agrees with the male contraceptive researchers who suggest that male contraceptives have been 10 years away for the last 50 years. He suggests that “it will be significantly more than 10 years before a hormonal or nonhormonal method for men that would be highly effective will be available in this country.” ■

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# New Male Contraceptive Options in the Pipeline

## Nonhormonal options included

There is a wide variety of potential male contraceptive products in the research pipeline. Hormonal contraceptive products have been studied a long time, but nonhormonal products also are under study.

Some early-stage products target sperm motility and hold potential as an on-demand contraceptive, says **Daniel S. Johnston**, PhD, chief of the Contraception Research Branch with the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, MD.

“If a man wants to be infertile for six hours, or if it lasts a couple of days, it’s a fascinating concept,” Johnston says.

These are some of the male contraceptive methods now under study:

- **Nonhormonal, reversible options.** In the past decade, various genes and proteins have been identified that are expressed in the male reproductive tract with deletion phenotypes that can lead to male infertility in mice. These phenotypes can arrest teratozoospermia, asthenozoospermia, globozoospermia, spermatogenesis, abnormal spermiation, and other outcomes.<sup>1</sup>

“You see a couple of on-demand, nonhormonal ones that have the possibility of being contraceptives if they can be successfully developed,” Johnston says. One candidate is in preclinical stages at Weill Cornell Medicine. (*See story on potential on-demand male pill in this issue.*)

Another possibility targets EPPIN, which is a surface protein on human spermatozoa. It is a sperm-surface drug target for male contraception.

This androgen-dependent gene is expressed in the testis and epididymis, vas deferens, seminal vesicle, and adrenal gland.<sup>2,3</sup> “These are trying to work their way to clinical trials,” Johnston says.

## Gel, Pill Under Consideration

- **Male contraceptive gel.** A clinical trial is underway for a male contraceptive gel that combines daily nesterone (NES) and testosterone.<sup>4</sup>

Study participants apply 2.5 mL of contraceptive gel to each shoulder and upper arm after showering in the morning. It is left on the skin for at least four hours before washing. Men and their female partners are enrolled in the study. In the efficacy phase, the sperm concentration is reduced, and participants continue to apply the gel so sperm concentrations are maintained at 1 million/mL or less. Enrolled couples agree to stop using other forms of contraception and only depend on the gel for pregnancy prevention. (*More information is available at: <https://bit.ly/2ElHlfo>.)*

- **Male birth control pill.** Daily oral dimethandrolone undecanoate (DMAU) is an active ingredient hydrolyzed to DMA, a novel derivative of 19-nortestosterone. It binds to progesterone receptors and androgen. (*More information is available at: <https://bit.ly/3g7wGmk>.)*

Another single-agent male hormonal contraceptive possibility is 11  $\beta$  methyl nortestosterone, which binds to the androgen and progestin receptors in vitro. (*Find out more at: <https://bit.ly/31dXmxi>.)*

Researchers also are working on a new molecule derivative of 19-nortestosterone. Early research suggested it could suppress testosterone and was well-tolerated in men when given in oral doses with food.<sup>4</sup>

- **Vas occlusion.** “Vas occlusion [methods] are interesting,” says **Heather Vahdat**, MPH, executive director of the Male Contraceptive Initiative of Durham, NC. “It’s beneficial to think of a reversible transition from vasectomy. Our partners in that space are developing different polymers injected into the vas.”

The injected polymers act like an implant and is administered in a similar way to vasectomy, which should make it easy for urologists to learn, she notes.

One option is Vasalgel, a multiyear contraceptive that is similar to a no-scalpel vasectomy. A gel is injected into the vas deferens. When a man wishes to restore the flow of sperm, the polymer can be dissolved and flushed out. (*Find out more at: <https://bit.ly/3gf2Bkl>.)* Another version, Echo-VR, uses a polymer hydrogel that is implanted inside the vas deferens. (*Find out more at: <https://bit.ly/2YgRBxe>.)* It is minimally invasive outpatient surgery that prevents sperm from traveling through the vas deferens, Vahdat says.

“They compare it more to an IUD [intrauterine device] because it’s in the reproductive organ, and it’s a physical thing that can be removed,” she explains. “These products are being designed to last for multiple years, fitting the role of a mid- to long-acting method.”

This contraceptive possibility could appeal to younger people who want to delay parenthood. “It is a set-it-and-forget-it mentality,” she says. “When you’re young, you don’t want to think about taking a pill every day, so it’s a great option.”

RISUG, developed in India, is another intravascular injectable male contraceptive that can make men sterile for 10 to 15 years. Animal models show that it is completely reversible.<sup>5</sup>

Recently, RISUG was approved in India, but as a permanent contraceptive solution and not as a

reversible contraceptive. “You inject it, and it becomes a permanent plug,” Vahdat says. “Downstream, they plan to make it reversible, but they got it to market as a permanent contraceptive.” ■

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# Fledgling Research Holds Promise for Safe, On-Demand Male Contraceptive Pill

*Anecdotal evidence suggests no side effects*

Researchers have found a possible way to target soluble adenylyl cyclase (sAC:ADY10), which is essential for male fertility. Using an acute-acting sAC inhibitor, an oral, on-demand, nonhormonal pill has the potential for temporary male infertility with no adverse effects.<sup>1</sup>

“If you take the sperm from a mouse, where this gene is knocked out, this sperm will never fertilize an egg,” explains **Lonny Levin**, PhD, professor at Weill Cornell Medicine in New York City.

The ultimate goal is to identify a sAC inhibitor that provides an on-demand contraceptive within an hour after dosing, while avoiding side effects.<sup>1</sup>

Men potentially could take the nonhormonal contraceptive pill at dinner, and their sperm would be inactive for at least a few hours, says **Jochen Buck**, MD, PhD, professor at Weill Cornell Medicine.

“By the next morning or day — we don’t know yet — it’s as if the pill was never there,” Levin says. “The theory is it would have no side effects.”

Their confidence in the potential of no side effects is based on the case of two Iranian farmers, who presented to an infertility clinic and were studied by investigators, Levin says. The men’s problem was described as a sAC knockout that rendered them infertile. Both men were married, middle-aged, and had no other health problems besides lacking an enzyme necessary for fertility. They had lived without this enzyme their entire lives.

“That gave us extreme confidence that people can live without this enzyme for some time,” Levin says. “It gave us even more confidence that if we have a man with an inhibitor for a few hours, there would be no problem because these two men lived

without the enzyme their whole lives.”

After learning of the infertile men’s case, Levin and Buck decided an on-demand, reversible, nonhormonal male contraceptive pill was possible.

“The only thing wrong with the two men is they have increased frequency of kidney stones,” Levin says. “But they’re two people who are living without the enzyme for their whole life, so we cannot imagine that living without it for six hours would do that. As long as you didn’t take the pill every day for 30 years, I don’t see it as being a problem.”

Traditionally, there has been less attention paid to the nonhormonal male contraceptive methods. This is why the Male Contraceptive Initiative (MCI) of Durham, NC, provides seed funding for this niche, says **Heather Vahdat**, MPH, executive director.

“The folks working in the hormonal space are doing great work,

and this was a good place for MCI to come in and put our focus,” Vahdat says.

The study, funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, employs a researcher who received a postdoctoral fellowship from MCI.<sup>1</sup>

“We’ll make a number of versions of this inhibitor,” Levin says. “We’re going to see when we have the fewest side effects.”

The goal is to find a version that produces no side effects and can last as a contraceptive as long as needed, he adds.

The research is one to two years away from a Phase I clinical trial, Buck says. “We started with a first-generation compound that was not

active enough. We first need a better compound.”

The Phase I trial would be designed to administer the drug and study participants’ sperm through an in vitro test. The Phase II trial would be similar, but a Phase III trial would look at the men’s real-life experience, Buck notes.

“We will need investors once we identify the compound,” Levin says.

Federal funding is necessary for the preclinical work to continue. “A chemist group can make compounds, but testing in mice is very expensive,” he says. “Without [federal grant] support, we couldn’t get to the promised land.”

If this male contraceptive approach goes through preclinical research and clinical trials to become an

on-demand pill, it could become very popular among men, Levin says.

“This is purely anecdotal because we haven’t done any studies,” Levin explains. “But one thing we do, as researchers, is present to graduate students and try to attract them to work in our lab. Every male student in the room’s eyes lit up, and we got a lot of students wanting to work in the lab because they think the potential is huge.” ■

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# Marketing a Male Contraceptive Plays Role in Availability

*Acceptability also related to side effects*

The marathon race for finding an effective and safe male contraceptive has reached a hurdle that was not as much of a barrier for the research race to bring the first female contraceptive to market: Someone needs to prove men want their own contraceptive and will use whatever method succeeds.

“Whoever comes up with the first male contraceptive, it’s going to be interesting to see how they market it and bring it to market,” says **Daniel S. Johnston**, PhD, chief of the Contraception Research Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, MD.

Hormonal male contraceptives must overcome the challenge of producing a product that changes the

body’s production of testosterone. These products can leave side effects that make them less appealing to men. Researchers have worked for decades to produce hormonal products that can stop sperm production, but reduce side effects.

“All of men’s hormones are tightly linked to sperm production. If you shut down one, you have to give him another,” says **Anita L. Nelson**, MD, professor and chair of obstetrics and gynecology at Western University of Health Sciences in Pomona, CA.

There are big differences in men’s sensitivity to hormonal contraceptives. “At research sites in China, they had [potential contraceptives] that would bring sperm counts down to zero, while the same [dose] in the U.S. would

bring sperm counts to the three-to-five million range,” Nelson explains. “Researchers have to look for a compound to be specific and to not overdose, and to give men a delivery system they will use.”

For instance, injections could work well. “But it’s not reasonable to ask a guy to come in once a week for an injection,” Nelson adds.

## Gender Roles Changing

Contraception has been an assigned responsibility for women for a long time, but that is beginning to change, says **Logan Nickels**, PhD, research director of the Male Contraceptive Initiative in Durham, NC.

“We are understanding that gender roles don’t have to be static over time,” Nickels says. “Men are starting to step up and have the ability to be more a part of these conversations.”

Previously, some men and groups were reticent to infringe on the bodily autonomy and rights of women. But now they understand there is a way they can build mutual understanding and common purpose when it is time to have a family, Nickels explains.

“It’s a process that takes two, and both parties should have some piece of decision-making and have tools to participate in the decision,” he says.

Some new surveys and studies suggest that the time may be right for bringing a male contraceptive to a receptive market.

For example, when the Male Contraceptive Initiative asked men ages 18 to 44 years about male contraception:

- 60% of men said they would like to take responsibility for birth control as a key reason for wanting a new male method;
- 80% said they would prefer a nonhormonal method, while 38% would prefer a hormonal method of male birth control;
- 89% said they wanted a reversible contraceptive method;
- 80% said it is important to have

a contraceptive method that also protects against sexually transmitted infections.<sup>1</sup>

“Another area we’re focused on understanding is the desires of young people,” says **Heather Vahdat**, MPH, executive director of the Male Contraceptive Initiative. “We assessed whether they would be interested in taking a pill before intercourse rather than taking a pill every day or using gel or an implant. The highest percentage of interest was in taking a pill before intercourse,” Vahdat says. “Everyone thinks, ‘Why should I take a pill every day for something I’m not doing every day?’”

Other research has assessed whether men would find certain types of contraceptive administration acceptable. For example, one study about a daily pill regimen — dimethandrolone undecanoate — found that 80% of participants reported satisfaction with the birth control method, and 77% would recommend it. In the trial, participants were randomized to receive up to four capsules daily vs. placebo. They had to ingest the pills within 30 minutes of eating a high-fat meal. Nine out of 10 male participants said they had no trouble taking the four pills within 30 minutes of the meal.<sup>2</sup>

Since there are many safe and effective female contraceptives on the

market, developing and marketing a male contraceptive has a higher hurdle. This is a development challenge funders are trying to address.

“Our research is trying to make more of an effort to bridge product developers and people who do marketing studies,” Johnston says. “We’re very interested and starting to commit more money — including a workshop this fall — to bring contraceptive product developers together with marketing people. How do you make people want to use these products?”

The National Institutes of Health can fund these early male contraceptive studies, but it will not sell the products, he says.

“We need someone in the industry to come in and invest in it,” Johnston adds. ■

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# Study: Women Use Female Condoms More When Their Partners Approve

Female (internal) condoms were hailed as a method that gave women control over their disease protection. But one factor was overlooked: Women's reproductive health decisions are influenced by male partners. A recent study revealed that having a partner with positive attitudes toward the female condom was associated with greater odds of women using the female condom.<sup>1</sup>

"Although the female condom is a method theoretically enabling women's sexual agency and bypassing the need for partner involvement, women still orbit under the influence of men," says **Joanne E. Mantell**, MS, MSPH, PhD, professor of clinical medical psychology at Columbia University Irving Medical Center in New York City. "Despite the hyperbole of women's control of the female condom and other prevention technologies, in some contexts, women prefer to inform their main partner of their precautionary measures."

Family planning providers should not underestimate how important male partner involvement and support are to sustained female condom use, says **Jennifer Ann Smit**, PhD, executive director of the MatCH Research Unit at the University of the Witwatersrand in Durban, South Africa.

"Communication with partners is a quintessential feature of healthy sexual relationships," Mantell adds. "Some women may feel compelled to disclose female condom use to their main partners out of fear that their partners would find out and accuse them of infidelity if they used the method covertly."

The study divided female university students in South Africa

between those who participated in a one-session, information-only, group-delivered minimal intervention and those who participated in a two-session, group-delivered enhanced intervention.<sup>1</sup>

Most of the study participants were in heterosexual relationships. Ninety-six percent reported having a main sexual partner, Mantell notes.

"Participants had an average of 2.4 sexual partners in their lifetime," she says. "Partners were, on average, four years older (24 years old) than the average age (20 years) of the study participants."

Both interventions focused on safer sex practices and reducing HIV and sexually transmitted infections (STIs). This is how the interventions worked:

- **Minimal intervention.** This 60- to 90-minute group session included information about personal vulnerability to disease and pregnancy, and ways to address these risks and handle problems, Mantell says.

It also covered the female condom's protection against HIV, STIs, and pregnancy. It showed women how to use, insert, remove, and dispose of female condoms. The education compared the effectiveness and use of male (external) condoms and female condoms.

Participants also received a brief review of the female reproductive system. Researchers used a pelvic model to demonstrate how the female condom was inserted, but they did not practice insertion on the model, Mantell says.

"Participants' perceptions of the female condom and anticipated problems with use were elicited during the session," she says. "The

intervention also sensitized women to the potential for partner abuse and provided guidance on assessing signs of potential abuse and risk mitigation strategies. Women were cautioned about possible dangers of initiating male condom or female condom use in the presence of these signs and were provided with referral sources."

- **Enhanced intervention.** The enhanced intervention included two group sessions that lasted four to five hours. These were grounded in social learning theory.

"It included the same information as the one-session minimal intervention, but also covered partner negotiation, skills in inserting and using the female condom, and personal goal-setting regarding HIV and pregnancy prevention," Mantell explains.

Mantell describes the main tactics covered in the enhanced intervention:

- Obtaining and maintaining a condom supply;
- Having condoms for use when needed;
- Negotiating female condom use with partners in a way likely to succeed;
- Overcoming objections, resistance, refusal, and violence that might be encountered;
- Using male condoms correctly;
- Using cognitive restructuring, behavioral rehearsal, and structured practice with feedback techniques;
- Increasing positive expectancies for female condom use by fostering positive peer norms;
- Providing encouragement and reinforcement through group social support.

"Women in both groups were given a supply of 10 female condoms

and 10 male condoms,” Mantell says. “The interventions were facilitated by study staff with nursing or social science backgrounds, trained and experienced in group facilitation.”

To avoid contamination across the trial’s arms, each of the interventions was delivered by a different interventionist. “The added strength of the enhanced intervention was the opportunity for learning of skills to negotiate female condom use with partners and skills in insertion and use of female condoms,” Smit says.

This provided the young women with the confidence to try female condoms and to overcome barriers to use, she adds.

“For me, the main strength of the enhanced intervention approach was that it allowed discussion and debate amongst peers and an opportunity to hear the views of peers and ask questions of facilitators and trained study peer educators, who also were students,” Smit says.

If the same trial were held in the United States, the findings might vary because context matters, Mantell and Smit say. “I believe that findings might differ across countries dependent on gender norms, women’s empowerment status, culture, and socioeconomic status of women, including education and employment income,” Smit explains.

“In countries like the United States, university students may be less influenced by partner attitudes to female condom use. However, since use of the female condom requires male partner knowledge of female condom use and cooperation in its use, positive partner attitudes may well be found to facilitate female condom use.” ■

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# Why Has the Female Condom Not Been Widely Adopted in the United States?

**C**ontraceptive Technology Update (CTU) asked two researchers involved in a new study about female (internal) condom use to answer some questions about the use of this contraceptive method in the United States. **Jennifer Ann Smit**, PhD, executive director of the MatCH Research Unit at the University of the Witwatersrand, Durban, South Africa, and **Joanne E. Mantell**, MS, MSPH, PhD, professor of clinical medical psychology at Columbia University Irving Medical Center in New York City, answered questions via email.

**CTU:** Why do you believe the female condom is not more widely used in the United States?

**Mantell:** This is for a number of reasons. First, the cost of the female condom in the United States and elsewhere is higher than that of the male [external] condom. Second, the female condom has not been adequately promoted to create

consumer demand. For example, a 2014 study revealed that only 48 of the 79 municipal and state departments of health websites examined referred to the female condom.<sup>1</sup>

In a 2012 New York state study of the female condom, we suggested that subsidizing female condoms and helping agency directors understand the need for the female condom and development of action plans may increase promotion of the female condom.<sup>2</sup>

Some discourse has marginalized the female condom due to its cost and the need to obtain partner cooperation. Policymakers and frontline providers often become enthusiastic about new prevention technologies and may promote them more vigorously than methods that have been around for a long time. Given that men may lack detailed information about the female condom and how it works, female

condoms need to be promoted to men. Most importantly, women often do not appraise that they are at risk for HIV and do not adopt any prevention measures. This also may be an underlying factor in women’s underutilization of oral PrEP [pre-exposure prophylaxis] in the U.S.<sup>3</sup>

**Smit:** The cost of female condoms is higher compared to male condoms.<sup>4</sup> There also may be difficulties in accessing female condoms.<sup>5</sup>

**CTU:** If you were discussing the study results with American family planning clinicians and gynecologists, what would you want them to know that might better inform their own practices?

**Mantell:** Choices matter. No one contraceptive method is the perfect fit for all women and their partners. There is a need for multiple methods of family planning and disease prevention with options counseling to enable family planning and OB/

GYN clients to choose what works best for them. These choices are likely to change over the lifetime as a function of age, achieving fertility desires, and partner status. OB/GYN practitioners should suggest women talk with their male partners about using the female condom for disease and pregnancy prevention.

**Smit:** Across the world, there are an array of contraceptive methods and an increasing number of HIV prevention methods available, but only condoms provide protection against STIs — the rates of which are persistently high. Female and male condoms are the only methods that provide simultaneous protection against STIs, HIV, and pregnancy — triple protection, if you like.

Female condoms offer another option to male condoms: they are a female-controlled method and it may

be easier for women to initiate use of female condoms than male condoms, sometimes introducing them as a contraceptive method rather than a disease prevention method.

Female condoms are preferred to male condoms by some couples, and some men and women find that they enhance sexual pleasure. Female condoms do not require a prescription to purchase, and can be made available in public places for easy access. There are several designs of new female condom products which have made them more attractive, acceptable, and pleasurable.<sup>4</sup> ■

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# Etonogestrel Contraceptive Implant and VTE in Postpartum Women

By Rebecca H. Allen, MD, MPH, Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

The current labeling of the etonogestrel implant (Nexplanon) suggests delaying insertion until 21 days postpartum because of the risk of venous thromboembolism (VTE). This study was conducted to ascertain the rate of readmission for VTE during the first 30 days after delivery in women with and without the etonogestrel implant. The investigators used data from the 2016 Healthcare Cost and Utilization Project Nationwide Readmissions Database, which included 36 million hospital discharges. Using ICD-10 codes, delivery hospitalizations were identified, as well as admissions containing a diagnosis code for both delivery and subdermal contraceptive insertion. Women with a history of

VTE or who were taking anticoagulation medications were identified and excluded. Further data were collected, including age, insurance, mode of delivery, medical conditions, and tobacco use. The primary outcome was the rate of readmission for deep vein thrombosis and pulmonary embolism in women readmitted up to 30 days postpartum with and without immediate postpartum etonogestrel implant insertion.

Analysis of the 3.38 million deliveries noted that only 8,639 (0.0025%) of these women underwent postpartum contraceptive implant insertion immediately after delivery. Women who received the implant were younger (25 vs. 29 years of age), more likely

to have public health insurance (82% vs. 43%), more likely to be smokers (15% vs. 6%), and more likely to have hypertension (22% vs. 12%). There were no differences in terms of rates of diabetes, thrombophilia, systemic lupus erythematosus, or cesarean delivery. A total of seven VTE cases occurred in the implant group compared to 1,192 in the non-implant group. There was no difference in the rate of VTE among those who received an implant and those who did not (0.85/1,000 deliveries vs. 0.35/1,000 deliveries; odds ratio [OR], 2.41; 95% confidence interval [CI], 0.58-9.89). The difference remained unchanged when adjusting for age, smoking history, peripartum infection, and

occurrence of postpartum hemorrhage (OR, 1.81; 95% CI, 0.44-7.45).

## Commentary

The U.S. Medical Eligibility Criteria for Contraceptive Use (USMEC) from the Centers for Disease Control and Prevention rates the etonogestrel implant as category 1 (no restrictions on use) in non-breastfeeding women and category 2 (benefits outweigh the risks) in breastfeeding women, for women less than 21 days postpartum.<sup>1</sup> This is in contrast to the current labeling for the etonogestrel implant as mentioned earlier. The authors of this study did not find any increased risk of VTE with etonogestrel implant insertion immediately postpartum, which supports the USMEC recommendations. The study does have limitations in that it only followed patients up to 30 days postpartum and there may be cases of VTE that occurred beyond that. The rate of postpartum VTE has been found to persist until 12 weeks, albeit dropping from nine per 10,000 deliveries in the first week postpartum to 0.1-0.2 per 10,000 deliveries in the 12th week.<sup>2</sup> Further, the study only examined inpatient readmission for VTE. There could have been subjects treated as outpatients, thus underestimating the risk of VTE. Additionally, database studies are limited by the accuracy of the discharge codes entered.

Further limitations include the number of VTE events found in the

study despite using a national database. Although the rates were consistent with other data, there still were only seven events in the etonogestrel implant arm, making the confidence intervals quite wide and, thus, less precise.<sup>2</sup> A post hoc power analysis indicated that the study only had 61% power to detect a difference between the two groups. Moreover, the study did not account for other contraceptive methods that women in the non-implant group might have been using in the immediate postpartum period, such as depot medroxyprogesterone acetate (DMPA), the progestin-only pill, or the levonorgestrel intrauterine device (IUD). Of these other progestin-only methods, only DMPA has been associated with a slightly increased risk of VTE in the general population in previous studies.<sup>3</sup> In a recent study examining DMPA use in the immediate postpartum period (within seven days of delivery), investigators found the risk of VTE to be slightly elevated compared to the control group (0.42/10,000 women-days vs. 0.15/10,000 women-days; adjusted OR 1.94; 95% CI, 1.38-2.72).<sup>4</sup> Nevertheless, the authors concluded that, although the OR was elevated, the absolute risk was very low, and the USMEC ratings stating the method was safe to use less than 21 days postpartum were appropriate. Providing contraception in the immediate postpartum period is an important option for patients for several reasons.

It is convenient, patients have health insurance coverage at that time, and they may not be able to follow up postpartum in the office. Overall, progestin-only methods are considered safe immediately postpartum. This study found nothing to contradict the ratings of the USMEC, and the drug labeling of the etonogestrel implant likely is more conservative than necessary. In our practice, we continue to offer our patients immediate postpartum IUD and implant insertion, DMPA administration, and progestin-only pill prescriptions. ■

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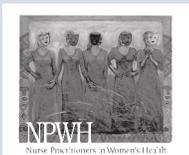
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## CME/CE QUESTIONS

1. **What are the main challenges in bringing a male contraceptive to market?**
  - a. Getting researchers and doctoral students to work on male contraceptive methods
  - b. Obtaining federal and state grants for preclinical projects
  - c. Marketing studies show that men are not interested and condoms are cheap
  - d. Funding and finding the right administration
2. **One male contraceptive candidate — daily nesterone and testosterone — which is furthest along in clinical trials, is a topical gel administered by:**
  - a. applying the gel to the abdomen.
  - b. applying the gel to the thighs and groin.
  - c. applying the gel to each shoulder and upper arm after showering.
  - d. applying the gel to the neck and back.
3. **According to the authors of a new study, women who use female condoms for protection against sexually transmitted infections and for contraception are more interested in this product when they are encouraged by:**
  - a. their families.
  - b. their healthcare providers.
  - c. their government through marketing campaigns.
  - d. their male partners.
4. **According to a survey from the Male Contraceptive Initiative, what percentage of men, ages 18 to 44 years, said they would prefer a nonhormonal method of contraceptive?**
  - a. 38%
  - b. 80%
  - c. 55%
  - d. 95%