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### A New Era Begins in Contraception: The Vaginal Gel pH Modulator

Announcer:

Welcome to CME on ReachMD. This activity, entitled "A New Era Begins in Contraception: The Vaginal Gel pH Modulator" is provided by Omnia Education and is supported by an independent educational grant from Evofem Biosciences, Inc.

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Dr. Eisenberg:

Use of contraception is nearly a universal experience in the United States. Unintended pregnancy rates remain high. With the recent approval of the vaginal pH modulator, there are now more contraceptive options than ever before. How will this new method fit into clinical practice?

This is CME on ReachMD, and I'm Dr. David Eisenberg.

Dr. Portman:

And I'm Dr. David Portman.

Dr. Eisenberg:

So, to start us off, Dr. Portman, can you give us a brief introduction to vaginal pH modulators or VPMS?

Dr. Portman:

Vaginal pH modulators are a new approach to on-demand contraception. We know that the normal vagina maintains an acidic pH, but it's never really been leveraged for contraceptive efficacy. This is a nonhormonal method, so keeping the vagina acidic even in the presence of alkaline semen makes a lot of sense physiologically. It's an on-demand method, which empowers the woman and allows it to be in her control as opposed to a male condom, which is often not so. And it's also an on-demand – used as needed, as opposed to combined hormone contraception, which requires either daily, weekly, or monthly use. So it does take the routine out of that, which often requires patients to be quite diligent in pill taking or patch application or ring use. So the idea of having a nonhormonal on-demand method with an ease of usage, particularly a prefilled applicator, is quite a novel approach to contraception.

Dr. Eisenberg:

Yeah, and I agree. When I'm talking with patients about the different contraceptive choices – as there are many women who do want to avoid hormonal contraception. But the other thing is, we have certain populations of women who – certain contraceptive methods might be less effective. And I know my population that I take care of in the Midwest, some of them are patients with underlying medical issues, or they have obesity and some of the medical concerns around contraceptive methods being less effective. And this really has no BMI restrictions. And other than people who might have allergy or sensitivity to the active ingredients, there really are no contraindications for the use of the vaginal pH modulator as I understand it.

Dr. Portman:

Now, that's a great point. Let's dive a little deeper. Dr. Eisenberg, please explain the mechanism of action for the vaginal pH

modulator. How does it compare to other contraceptive methods?

Dr. Eisenberg:

You know, it's actually very novel. It's a combination of three active ingredients in Phexxi. It's lactic acid, it's citric acid, and potassium bitartrate in a gel that has a bioadhesive property so that each single-dose vaginal applicator contains about 5 grams of gel, of which 90 mg of the lactic acid, 50 mg of citric acid, and 20 mg of the sodium bitartrate are the active ingredients, with some inactive ingredients that are really important to keep this as a dense, uniform consistency that, when the patient uses the self-contained, prefilled applicator and administers it up to an hour before each active vaginal intercourse, it stays in the vagina because it has a viscosity and a bioadhesive property to the vaginal epithelium that appears to be persistent and present in the vaginal canal for up to 12 hours.

And it really does a fantastic job of maintaining that vaginal pH in an acidic environment at 3.5 to 4.5 even in the setting of ejaculate, which we know the sperm and semen that's present in ejaculate raises the pH, allows the sperm to maintain viability and motility to be able to then ascend the cervical canal and into the uterine cavity and out to the fallopian tube, potentially fertilizing an ovum. And in this case, with the vaginal pH modulator in the vagina at least an hour before intercourse, you're going to have immobilization of that sperm in a way that women are less likely to get pregnant.

And when you think about kind of effectiveness and efficacy, I think that's an important concept that I hope we'll touch more on. But when I talk to patients about this, I really put this in the same category as barrier methods they're used to talking about, things like male and female condoms. And we think about the tiered contraceptive methods that many people are familiar with, it's in that less effective tier, but still has a typical-use failure rate of about 11% over the contraceptive trial that the FDA reviewed before approval.

Dr. Portman:

Now I think those are all excellent points and a great overview to the mechanism of action. I would also add that, you know, in addition to maintaining this acidic pH, we know that that helps maintain the normal vaginal flora, which is important for vaginal health, but also that environment may reduce the transmission of STIs, the most common being chlamydia and gonorrhea. In fact, the phase 2 study of the vaginal pH modulator noted a 50% reduction in chlamydial infection and a close to 80% reduction in gonorrhea infection. This needs to be borne out in a larger phase 3 trial, which is currently ongoing. But it's very exciting, as you mentioned, that similar to the other tier 3 contraceptives which offer those non-contraceptive benefits of STI reduction, it'll be very interesting to see how this bears out in future trials.

Dr. Eisenberg:

For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. David Eisenberg, and I'm here with Dr. David Portman. We're discussing the recent approval of the vaginal pH modulator and its role in clinical practice.

Dr. Portman:

Let's transition a little bit. There's been significant clinical trial results on the contraceptive effectiveness of the vaginal pH modulator. Dr. Eisenberg, what have these studies found in terms of its efficacy and adverse events?

Dr. Eisenberg:

You know, an important thing that we talk about as we generally tend to think about contraceptive methods based on a number of different markers of effectiveness. And, you know, the Pearl Index is just one of those markers. The Pearl Index is, of course, defined as kind of a perfect use under ideal conditions. And in patients who were using the vaginal pH modulator in the seven-cycle study, the Pearl Index was 27.5. Now, that sounds high, but when you think about what that really means, given the understanding of the way in which the Pearl Index is calculated, it's very similar to patients using other barrier methods like condoms, male and female condoms. And, in many ways, when I talk to patients about effectiveness and efficacy, I really prefer using the understanding of kind of the typical-use cumulative pregnancy rate, which is generally calculated through life table analyses. And, in that case, when you look at it that way, the failure rate was 13.7% over seven cycles. Again, very similar to barrier methods like condoms.

The other thing that I think is important, and you know this in talking with patients about contraceptives, it's not just about how well does it work, but you know, am I going to have any concerning side effects? Am I going to have any difficulty with using it or being able to follow the directions? And it was actually interesting that in the subjects in the original phase 3 trial, increasing satisfaction was seen over the duration of the trial where nearly 90% of subjects were very satisfied at the fourth visit compared to, say, 46% in the initial visit after the study drug was dispensed. And when you look at that rising satisfaction over time, I think that has a lot to do with people's comfort with how to use the vaginal pH modulator.

And there wasn't any concern with regards to things like sexual satisfaction. Women in the second phase 3 trial reported improvement in sexual satisfaction and function after just one cycle of the vaginal pH modulator compared to baseline. And most subjects reported improvement in their ability to maintain lubrication during intercourse and other measures of sexual function, which were, I think,

important things for the investigators to be looking at.

Dr. Portman:

So this is unique in some trials that really don't even measure those parameters. So, to see an improvement in sexual satisfaction largely based on the lubricating effects of this gel is quite important. Another issue that you brought up is the efficacy and effectiveness, and there were over 24,000 episodes of vaginal intercourse in the trial. And based on the effectiveness of this on-demand method, the failure rate per sexual encounter was 0.4%. So to tell a patient that an on-demand method is close to 99+% effective for that individual act, which she's largely using that method for, could be quite reassuring as opposed to the quite high Pearl that you mentioned.

Dr. Eisenberg:

Yeah, and I think one other thing that I failed to get into was just talking with you about the adverse reactions that were reported in these large trials. I think it's important to realize that there were two phase 3 studies combined that represented over 2,800 subjects in over 19,000 cycles of exposure. So, like you pointed out, very robust data. And only 1.6% of subjects discontinued participation in the clinical trials due to an adverse reaction, which is a very low discontinuation rate for any contraceptive trial, for that matter. And the kinds of adverse reactions that subjects had were not unsurprising to me, things like a burning sensation or an itching sensation during application, and you know, other kinds of vulvovaginal discomfort, bacterial vaginosis, and vaginal candidal infections. Things that are not unusual with just regular sexual activity regardless of the use of a contraceptive gel like a vaginal pH modulator.

So, in keeping with the discussion on the clinical trials, Dr. Portman, can you discuss a little bit more about the impact of contraceptive trial design, and how contraceptive effectiveness is measured and how we communicate that?

Dr. Portman:

Yeah. This is, I think, a really important subject for our listeners that – they may have become very accustomed to artificially low Pearl Indices. So there's a real disconnect between clinical trial efficacy and real-world effectiveness. So I think that this particular trial of the vaginal pH regulator is so important because it really did look at real women – no restrictions on BMI. We know that an elevated BMI can decrease contraceptive efficacy, certainly when it comes to hormonal contraception. The fact that this is a very representative population, diverse ethnically as well as by weight, is so important for us to have good, real-world data to share with our patients. They've also broken down, for this particular trial, those who adhered to the protocol, those who were either using backup method, and other factors that do affect patients in the real world. And the range, as you mentioned, in looking at the perfect use, may have been closer to 6% failure rates versus the 13% rate. So it's really important for us to – and when we counsel patients, to say that we know that the real world happens, and you may be using different methods, backup or not, and to be able to relate this data in very compelling ways and not just simply old clinical trial data, but real-world experience. And I think that's really what this trial, as well as future trials, need to do is give us generalizable information that's very understood by our patients.

Dr. Eisenberg:

Yeah, I think it's really important to make that point, that as a provider of sexual and reproductive healthcare services, but also as a researcher in this phase of bringing new contraceptives to market, I want to make sure that the patients I'm taking care of in my everyday practice are reflected in the patients who are enrolled in these contraceptive trials to make sure that it is applicable, and I think that's really important.

So, this has certainly been a fascinating conversation, but before we wrap up, Dr. Portman, can you share with our audience your one take-home message?

Dr. Portman:

Women need a variety of options, and ultimately, they're going to choose what works best for them. So we know that one size doesn't fit all. If the only tool in your toolbox is a hammer, then everything looks a nail, and we can't really force patients to use methods, whether we think that they're more highly effective than another, if it's not going to fit with their lifestyle. So I think an on-demand vaginal pH regulator that empowers women to take their sexuality and their contraception into their own hands is a great advancement.

Dr. Eisenberg:

I agree. Lastly, I'll just say that I'm really hopeful that the data regarding the reduction in STI acquisition really pans out over the next few years and that we can offer our patients additional advantages to the vaginal pH modulator beyond just the contraceptive effectiveness.

Unfortunately, that's all the time we have today, so I do want to thank our audience for listening in, and thank you, Dr. Portman, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Portman:

Thank you, Dr. Eisenberg. I really enjoyed the conversation.

Announcer:

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