Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/contraception-focus-vaginal-ph-modulation/12608/

Released: 06/11/2021
Valid until: 06/11/2022
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Contraception: Focus on Vaginal pH Modulation

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Contraception: Focus on Vaginal pH Modulation” is provided by Omnia Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Eisenberg:
Thank you for joining us for this educational program. My name is Dr. David Eisenberg. I am joined today by Dr. David Portman. We’re going to be discussing new developments in contraception getting into the details about the newest class of contraception, which is these vaginal pH modulators – the only vaginal pH modulator that is available now. And we’re going to talk a little bit more in depth about the mechanism of action and review the data from the clinical trials that the FDA looked at before granting approval of this new contraceptive.

So when it comes to the mechanism of action, I think we have to take a step back and recall that the vaginal pH is maintained by the microbiome of the vagina. There are lactobacillus there that ferment glucose, increasing lactic acid. And in general, a healthy vaginal pH is between 3.5 and 4.5, and this provides many advantages for people with vaginas, for women to avoid infections. And in the space of people who want to get pregnant, sperm are traveling with many different proteins and fluids associated with the semen in the ejaculate that helps raise the pH and allows for sperm to become capacitated and capable of swimming forward in the birth canal up into the cervix, through the cervical mucus, and out into the fallopian tubes by way of the uterine cavity. And when that sperm is exposed to that vaginal pH, it would be incapacitated if the semen didn’t have these buffering proteins to prevent for the acidic environment to incapacitate the sperm. And that really is an important process by which fertilization happens and sperm are able to get to the egg, but it is also a part of the processes that are probably involved in sexually transmitted infection acquisition. And so drugs that maintain an acidic pH in the vagina not only provide potentially for contraception mechanism of action, but also a potential mechanism to reduce STI acquisition. And the only spermicidal lubricant or spermicidal product on the market today – or prior to this new vaginal pH modulator, was a detergent known as nonoxynol-9. That spermicide can be disruptive to the vaginal mucosa and actually potentially increase for STI acquisition. So having a new product, a vaginal pH modulator, that is capable of keeping the pH at an acidic environment can neutralize sperm and have some additional advantages.

So to be a successful vaginal pH modulator as a contraceptive, not only does it have to maintain the pH, but it has to have a thick enough viscosity to prevent dilution in the setting of seminal secretions and vaginal secretions during intercourse. And it has to have this third property, this bioadhesive property to stick around in the vagina for enough time for the sperm to be exposed to become incapacitated according to those timelines we were just looking at, based on that previous work by Zhou et al. And many products have been tried. The vaginal pH modulator that was recently FDA-approved called Phexxi is a combination of lactic acid, citric acid, and potassium bitartrate. The potassium bitartrate, lactic acid, citric acid combination was approved in 2020 as the first-in-class vaginal pH modulator for contraception. And this idea of it sticking around is one of the big advantages of Phexxi over other pH modulators that have been investigated.

The lactic acid, citric acid, potassium bitartrate gel does require a prescription, and it comes in a box of 12 prefilled applicators. It has no

hormone, it is coitally dependent, meaning that a person that is not having sex regularly and doesn't necessarily want some of the side effects of hormonal contraception can use this only when they need it, on demand. It does need to be used prior to each act of intercourse. It is not a post-coital or emergency contraceptive method. There are those available in the United States. But it can be used in combination with other contraceptive methods, and essentially all but the vaginal contraceptive rings. And that's really just about the trials that were done which we're going to dig into in just a second here, because the trials had a contraindication for the use of a vaginal ring, according to the protocol. We just don't know whether it would be adequate in the setting of a contraception vaginal ring. But in other contraception methods, whether it's the pill, the patch, the shot, the implant, the IUD, male or female condoms, diaphragms, etc., the vaginal pH modulators can be used in combination with those.

So, let's talk about the contraception trial data. So this is a little bit more complicated because the FDA had two phase 3 trials worth of data to look at. The first trial, the AMP-001 protocol was a 6-month, 7 menstrual cycle, open-label, multicentered, randomized controlled trial of this vaginal pH modulator, now known as Phexxi, versus an FDA-approved nonoxynol-9 product known as Conceptrol. And you can see there, it took 3 years for this study to be run. And there's a lot of reasons behind why this was such a challenging trial, but this was designed based on the FDA's input and based on their recommendations for how contraceptive trials should be run.

But basically, you had a contraceptive cohort of 18- to 35-year-old women who – a little over 1,600 women in each arm, the vaginal pH modulator arm versus the nonoxynol-9 arm. And they looked at the cumulative pregnancy rate over those 7 menstrual cycles, or for 6 months, and the cumulative pregnancy rate was 10.5% with a 95% confidence interval. That's pretty tight there, as you can see. And what you can see in that next bullet point is that most users were correct and consistent. And when you specifically analyze the pregnancy rates amongst those correct, consistent users, the pregnancy rate was much lower,

Now, you do see that over half of the people in the arm discontinued within 6 months. That's a little problematic. And when you look at the nonoxynol-9 arm, it's pretty similar, both pregnancy rates and the discontinuation rates. Asking subjects to use these contraceptive methods as their only contraceptive method for 6 months did not work out well for a lot of these subjects for all kinds of reasons. But it's not because of adverse events. As you see, this last bullet point, less than 2% of either arm identified an adverse event as the reason they discontinued. The reasons for discontinuation were much more varied and not specific to adverse events. So the FDA basically went back to the company trying to bring this new vaginal pH modulator to market as a contraceptive and said, "We want you to redo a trial in a different way and specifically just an open-label, single arm, multicentered trial. You don't have to have a comparator and prove the contraceptive effect in that method." And what they did between July of 2017 and November of 2018, a much shorter time frame, they recruited over 1,300 18- to 35-year-old women, and they actually identified women as having regular menses. People who have regular menses, in general, are going to be ovulatory, they're going to be fertile, and they also had to be women who were willing to engage in at least 3 acts of heterosexual vaginal intercourse per cycle.

And so what did they show? They showed in a really pretty tight confidence interval about 13.7% cumulative pregnancy rate over the duration – over that 7-cycle, 6-month trial, which is similar to many of the other barrier methods and coitally-dependent methods that we think of for contraceptives, like male and female condoms and diaphragms and things like that.

Now the FDA bases approval of contraception based on Pearl Indexes, and Dr. Portman is going to really do a great job of helping us understand Pearl Index versus survival curves as how we understand contraceptive effectiveness. And a Pearl Index of 27.5 sounds pretty high, but what you have to understand is that's pretty typical for these coitally-dependent methods, and again, going back to the discontinuation. Just to point out, only 1.6% of subjects throughout the 7-cycle, 6-month trial discontinued due to an adverse event. And subsequent analysis of the data looking at those perfect users, again, kind of thinking about, "All right, well, not everybody's perfect," the typical failure rate is about 11.3% in a separate analysis, slightly lower than the total cumulative pregnancy rate that you saw higher up on the fourth bullet point there. But amongst perfect users, no surprise, the failure rate is lower.

As we look a little more in depth about the trial, this is Table 1 from the publication that came out in 2020 in *Contraception* looking at the characteristics in the women enrolled in the study, on average, the mean age was 27.7 years +/- 4. I will point out that the race/ethnicity profile is pretty similar to the United States demographics, which is really a strength of this study. It's very generalizable. Again, if you look at the body mass index, the average patient enrolled was overweight, which again, pretty typical for the United States, right, and you can see as you move down into Table 1 here that a large percentage of the patients had been pregnant in the past. And so 449 people completed the entirety of the trial, and the effectiveness – or I should say efficacy analysis was based on the modified intention-to-treat population of a little over 1,000 women. And so as we look at this data, the trial not only included the subjects saying that they would be willing to have vaginal intercourse at least 3 times a month, but we asked them to keep track in a prospective manner of their vaginal intercourse events. And the acts of vaginal intercourse are recorded here, and what you see is amongst that modified intention-to-treat analysis, that there was a 13.7% cumulative pregnancy rate,

Lastly, I just want to touch on the satisfaction and side effect profile. The adverse events that occurred in this trial were pretty typical

things you'd expect with something like a vaginal pH modulator. Things like localized burning or itching, vaginal yeast infections, urinary tract infections, and other kinds of discomfort in the general area were not uncommon. But that being said, the majority of people who had these reactions classified them as mild, and less than 2% of people discontinued because of side effects. I will point out that the FDA added to the package label to avoid the use of Phexxi in women with a history of recurrent urinary tract infections or other known urinary tract abnormalities because of the fact that there was a small number of people who had urinary infections and one serious adverse event of someone who was hospitalized with pyelonephritis.

Lastly, the satisfaction over time really increased. And so what you're looking at here is a graph from the publication that came out last year, looking at, again, the enrollment versus visit 2 in the first, visit 3, visit 4, visit 5, as you move left to right. And the y-axis is the percent of women reporting that they were very satisfied or somewhat satisfied versus the people who were dissatisfied. And what you see is the satisfaction rate really increased over time compared to the first cycle and compared to baseline. And most subjects said that they would continue after the trial and recommend to a friend, which I think is something that's important to think about as you talk about successful contraception.

I'm curious to hear from you, David about how you think you will talk to patients and help educate them about this new contraception method.

Dr. Portman:
What I'd like to try to do is discuss some of the evolution of some of the clinical trial design and the contraceptive field, how this has really impacted the way we counsel patients about how truly effective a method is and see whether or not we're moving towards some consistency in design, as well as the way we can contextualize this for our patients.

And we're going to get into how do we come up with these numbers, because many of us have been mistakenly counseling patients based on really false Pearl Indexes from older trial methodology, which gave us a false sense of efficacy, nearly 99% effective with a Pearl Index in the low single digits or less than 1. And so I think we really have to reorient how truly effective these methods are in the real world. Now I don't think any of us when we talk to patients really understand how to contextualize that for that patient in front of us, so I think that we really have to move away from the Pearl Index as a useful counseling tool and also recognize that the historical Pearl is very low. Pearl Indexes in trials done 2 or 3 decades ago were largely because they were long and therefore, if you have an infinite number of cycles, you're going to drive the Pearl down to close to 0. They often didn't capture actual sexual activity. They recruited European, thin females who had already had their 1.2 children and were highly motivated to use contraception in a very continuous way, and also with restrictions on enrolling patients of overweight or obese BMIs.

We know that all of these factors, if we look at them in the modern setting, have led to what has been called the "creeping Pearl," which Dr. James Trussell and I coined in a paper we published on contraception in 2013. And we found that there were multiple factors that really led to this creep in the Pearl Indexes from below to many of the trials showing Pearl Indexes in the 3, 4, and now the even 5 range. So are these contraceptives getting less effective over time? I would say absolutely not. It's really the fact that trials have changed, enrolling patients who have higher BMIs, more diversity, more aggressive capturing of pregnancies, and excluding cycles that may have been included previously. And this trend was clearly identified in this slide where you see that the patch of the low-dose levonorgestrel patch was approved with a Pearl Index of 5.8. I presented to the FDA advisory committee for this particular product, and it was very clear that the trial design was highly impactful of this Pearl Index. And yet the need for a low-dose transdermal patch option was great and the benefits clearly outweighed the risk, and this Pearl Index was put into that context.

Here you see the segesterone vaginal ring with a Pearl Index approaching 3. Interestingly, if you look at subgroups of that ring, the patients in Europe had a 5-fold lower Pearl Index than the US cohort. Hispanic patients had higher Pearl Indexes, as did younger patients. So depending on the population, efficacy and effectiveness are very variable, and that's why it's so important to have trials that are representative of the kinds of patients that we're counseling.

So when it gets down to counseling, though, I think patients don't want to get lost in the weeds. They may not really care about these historical trends. They want to know, overall, is this the right contraceptive for me based on all the factors that we discussed earlier, and is it reasonably effective

So lastly, how does this evolving clinical trial landscape impact a very novel trial design which David discussed in the Phexxi development program? And as was mentioned, it has a risk of pregnancy of 13.7 over seven cycles. So if we flip that and could counsel patients this is 86% effective over seven cycles, that's certainly falling within that tier 3 category Pearl Index of 27.5. Sounds awfully scary, but if you look at this as a contraceptive that's an on-demand contraceptive where there were over 24,000 acts of intercourse and roughly 100 pregnancies, the chance of pregnancy per act of intercourse really translates into about 0.4%. So if a patient is going to be using this intermittently, that's going to be a highly effective method and a discreet method the patient controlled. And that may trump these types of numbers that might be off-putting to clinicians who are used to these very artificially low Pearls that we've seen

historically.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Omnia Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Omnia. Thank you for listening.