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Expanding Contraceptive Choices for Women: The Vaginal pH Modulator

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Expanding Contraceptive Choices for Women: The Vaginal pH Modulator" was presented during Omnia Education's Women's Health 2021: Beyond the Annual Visit.

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:
Welcome to Omnia Education's Women's Health 2021: Beyond the Annual Visit. Thank you for joining us today. My name is Dr. David Eisenberg. I am an associate professor in the Division of Family Planning in the OB-GYN department here at Washington University School of Medicine in St. Louis. In this presentation, we'll be taking a closer look at new contraceptive choices for women.

So quickly, our learning objectives. At the completion of this educational activity, learners will be able to, number one, explain the advantages and drawbacks of vaginal pH modulation contraception. Number two, identify the strategies that will overcome the most common misperceptions that both clinicians and patients have regarding gel-based contraceptives. And number three, discuss the scientific data underlying the increasing pregnancy rate demonstrated in contemporary clinical trials of contraception.

So as far as new hormonal contraceptives go, it's really a wonderful time to be an expert in contraception and a women's health provider in the United States, as far as I'm concerned, because we have so many more choices coming to the menu of options that people can have as a person who doesn't want to get pregnant. And one of the most exciting ones for me is the vaginal pH modulator that we're going to talk more at length about, but I want to just touch on the few new introduced methods in the last year or so.

The drospirenone-only contraceptive pill, brand name Slynd, is a really wonderful advancement for us to have a new progestin-only contraceptive pill in the United States. It's a 24/4 formulation and it has a very long half-life, which we'll look at kind of side by side with the progestin-only pill that most of us know, norethindrone.

The levonorgestrel and ethinyl estradiol patch, brand name Twirla, is the newest contraceptive patch available in the United States, and it's a 30-microgram ethinyl estradiol patch and similar to many of the combination or hormonal contraceptive pills, the patches, and the rings that we're all familiar with, but we'll talk more about that in detail.

Lastly is the new contraceptive ring, which is Annovera as a brand name. This is a new progestin called segesterone acetate, and it's at 150 micrograms with a daily dose of 15 micrograms of ethinyl estradiol. And it, too, behaves like most of those combination hormonal contraceptives that we've come to be experienced with in our practice. But I think it's important to understand the differences between this and the previous contraceptive ring that was available in the United States.

As far as the new progestin-only pill, many of us have been prescribing the 0.35-milligram norethindrone pill for patients who have a contraindication to estrogen, for people who are breastfeeding, and we know that the progestin component inhibits ovulation. But given the short half-life of norethindrone, people have to be really good about taking this medication at the same time every day. Otherwise, they have more side effects, specifically bleeding problems. Whereas the drospirenone-only pill, Slynd as the brand name, has 4

milligrams of drospirenone, which is more than most of the combination hormonal contraceptive pills with drospirenone in the United States. And that long half-life of drospirenone not only reliably inhibits ovulation, but it likely provides better cycle control for those patients who are maybe not perfect at taking the pill at the same time every day.

And like the progestin-only pills that you know, the contraindications and indications are the same.

As far as the new contraceptive patch, Twirla which is the brand name patch, has a different shape and slightly larger surface area than the Xulane or Ortho Evra branded patch that you may be familiar with. And the other key difference is the progestin. While it is a similar estradiol dose of ethinyl estradiol, about 30 micrograms versus 35 micrograms per day, it is a levonorgestrel-based progestin rather than norelgestromin, which, you know, the fact of the matter is some patients might find different side effect profiles with these different active ingredients. The larger surface area may be of concern for some patients. And the other thing that I will point out is that there is a black box warning associated with those patients who are obese and caution with patients who are overweight for reducing contraceptive success rate. We'll talk about those failure rates in detail at the end and how those are calculated for different contraceptive methods.

When you look at a side-by-side comparison of the new vaginal contraceptive ring, branded Annovera, you can see from the picture not only is it a thicker ring, but it is slightly wider in dimension. That thicker ring allows there to be 2 reservoirs of the active ingredients, but it is a different progestin. Whereas the NuvaRing and its generic versions have etonogestrel as the progestin, this is a new novel progestin called segesterone acetate and at 150 micrograms per day. And the ring itself is highly effective as a combination hormonal contraceptive, and it was FDA-approved in a phase 3 trial, where patients were putting the ring in for 3 weeks and taking it out for a week to let themselves menstruate. But there is enough hormone in that single ring to go for a full calendar year.

But there are a lot of folks out there who don't like hormonal contraceptives, and that's why I'm really excited about this new contraceptive method, a vaginal pH modulator. Vaginal pH modulation may be something you're not familiar with. And I'm going to take the opportunity to hopefully help you understand how this works and help you communicate with your patients about this because in my experience, patients when they come to understand this really like the idea behind this contraceptive, as a female-controlled, hormone-free, use it in the moment kind of contraceptive that they don't have to be taking on a regular basis.

And so this was FDA-approved as a hormone-free gel, and the picture you see here on the screen is of the prefilled applicator that many people will think, “Well, gosh, that looks like a tampon applicator.” And that's exactly how it's designed. The patient will deliver this gel into her vagina prior to the act of intercourse. And what it does is it maintains that vaginal pH in an acidic environment between 3.5 and 4.5 to create an environment that's inhospitable to sperm, and that is the primary mechanism of action. You know, the combination of 3 active ingredients in Phexxi, the brand name of this new vaginal pH modulator, is lactic acid, citric acid, and potassium bitartrate. But that's not the only components that are really important here. We have to talk about the fact that this new contraceptive gel “sticks” around for a while, and we'll get to that in a minute.

But this prefilled applicator is about 4 inches long, similar to a tampon as I said. They come in prefilled applicators which are wrapped individually in a box of 12 if you prescribe this to a patient. We have to make sure that patients understand that this, like a barrier method such as a diaphragm or a condom, whether it be male or female condom, has to be put in the vagina prior to the act of intercourse, or put on their partner's penis for a male condom, for example. And they need to apply the vaginal gel up to an hour before intercourse. They need to understand that if it's been more than an hour since they put the gel in and there's not vaginal penetration, they need to re-dose. Just like if they were going to have more than one act of intercourse, they would use a second condom, well, they need to re-dose if they have more than one act of intercourse in a short interval. And it was originally approved as a personal lubricant during intercourse. And so there's a long safety track record here. But it has been now FDA-approved based on a phase 3 trial that I was lucky enough to be a part of that demonstrated its contraceptive effectiveness, and we're going to talk about that more in detail.

As far as the mechanism of action goes, this is very unique compared to most contraceptive methods. So we know that the normal vaginal pH should be below 4.5, and that acidic pH is maintained by the normal healthy vaginal microbiome and the hydrogen peroxide and lactic acid that lactobacilli produce. That natural acidic environment is the vagina’s defense against infection, but during ejaculation sperm and the seminal fluids raise that pH to a point that sperm are able to capacitate and start swimming upstream towards the cervical canal, into the uterine cavity, and out to the fallopian tubes in the hope of identifying and fertilizing an ovum. In this situation where a patient has applied the vaginal pH modulator prior to intercourse, the vaginal pH stays in that acidic space where those sperm don't get the opportunity to swim. And it works really well to neutralize those seminal fluids because of its buffer capacity and the way in which those 3 active ingredients work together to maintain that acidic environment.

And currently it's under investigation as an antimicrobial, and we hope to see really promising data in the near future regarding that indication for use, but currently, it's only indicated for contraception.

So this is the key graph regarding the pH of the vagina in the setting of this vaginal pH modulator. What you see on the left is the total progressive motility of sperm from a proven fertile sperm donor, according to WHO fertility guidelines regarding sperm motility and sperm counts at different pH levels. And then across the x-axis there, you see time. So we need time of the sperm to be exposed to that acidic environment to incapacitate those sperm for forward motility. And at the red line along the bottom, what you see in total motility on the left and progressive motility in panel B on the right, in that pH 5.2 or lower, by 90 minutes, there was essentially no motility. The vaginal pH modulator Phexxi not only maintains that vaginal pH, but it sticks around long enough to incapacitate those sperm so they can't get to the ovum. That's its primary mechanism of action.

And when you look at this vaginal pH of the woman or person who's used Phexxi compared to the pH of semen, you see that significant difference on the pH scale there. But the reason it works so well is not only by maintaining that pH in the vagina, but like I said, kind of sticking around because it has a thick viscosity and bioadhesive properties that maintain it within the vaginal canal in a way that it adheres to the vaginal epithelium before then sloughing off in a natural fashion and being discharged from the vagina in a way that was not bothersome to participants in the study. The combination of lactic acid, citric acid, and potassium bitartrate with those bioadhesive properties allowed for the FDA to provide for an approval of a new class of contraceptive methods that we're calling vaginal pH modulators.

And so I mentioned this idea of the Phexxi sticking around. There have been many contraceptive gels that have been tried not only as contraceptives, but also as antimicrobials. And again, Phexxi is currently approved as a contraceptive. These gels show different levels of viscosity, different bioadhesive properties, but the bioadhesive properties and viscosity of Phexxi was kind of the sweet spot, meaning that the prolonged exposure of sperm to that acidic environment because of Phexxi allowed for a reduced fertility rate, a reduced pregnancy rate. And as I mentioned earlier, this has been around in the United States, FDA-approved in 2004 as a personal lubricant. So this has a really long safety record.

So the combination of lactic acid, citric acid, potassium bitartrate, and the non-active ingredients you see here, in a prefilled applicator allows for people who have a vagina who don't want to get pregnant, who don't want to use hormonal contraception, who don't want to use something on a daily basis, if they're not needing it, to have a new choice as a contraceptive method.

And again, this does require a prescription. It is important to emphasize, however, that patients using this vaginal contraceptive gel need to use it prior to the act of intercourse, up to one hour before vaginal penetration. Re-dose if it's been more than an hour, and re-dose if it's more than one act of sexual intercourse. It can be used together with condoms, diaphragms, cervical caps, other hormonal contraceptives, and IUDs.

I'll note that the FDA pointed out that the drug trial for Phexxi did not allow people to use the vaginal contraceptive ring. And so there is currently a contraindication to the vaginal contraceptive ring plus Phexxi because we just don't know how those things interact.

So let's talk about that trial data. As I said, I was lucky enough to be one of the principal investigators on a local site here in St. Louis through our Planned Parenthood affiliate.

There were two large phase 3 trials for approval of Phexxi as a contraceptive method. The initial one, AMPOWER-001 was a 6-month, 7-cycle, open-label multicentered, randomized controlled trial of the vaginal pH modulator versus our known nonoxynol-9 spermicide that’s available in the US market.

Now remember that nonoxynol-9 is a detergent. And that's how it works to prevent sperm from being able to get to the egg. However, it also provides for potential vaginal epithelial disruption in the way in which it behaves inside the vagina. And that is not a good thing to have in patients who are potentially at risk for a sexually transmitted infection.

And so the population of people who were in the trial were 18 to 35, there were over 1,600 subjects in each arm, and the cumulative pregnancy rate at the end of 7 cycles, or 6 months of use, with those participants solely using the vaginal pH modulator was 10.5%. And you see that confidence interval was pretty tight. And there was about 7 out of 10 people who were correct and consistent users. And when you look solely at those correct and consistent users, those perfect-use patients, we had a 4% pregnancy rate with, again, a very tight confidence interval.

But, I will note that more than half of the people in this trial discontinued at less than 6 months. That's similar to the discontinuation rate amongst those people enrolled in the control arm using the nonoxynol-9 product. But the pregnancy rate was also similar. And so the reason why people discontinued in the trial, however, was a lot of times lost to follow-up or other problems, not as you note in this last bullet point – not the majority of the time for discontinuation for adverse events. And we'll talk about the adverse events and side effects that people had. But that initial trial was really promising. And the FDA said, this is a reasonable product, but we need more data with longer continuation.

And so that's why AMPOWER-002 was done. And this was a similar phase 3 trial, open-label – patients knew what they were using, rather than a randomized control trial – single arm, there wasn't a control. Again, 18- to 35-year-old people, but this time we really selected for those people who were potentially fertile, either having super well-controlled regular menstrual cycles 21 to 35 days in length, and those participants in this open-label trial had to agree to have at least 3 acts of heterosexual intercourse with a male partner for every cycle. And if they didn't, we had to throw out that month's worth of data. And so this contraceptive trial really was a trial of the vaginal pH modulator as the only method.

Again, in that typical-use, all-in population of a little over 1,300 women, the pregnancy rate was about 13.5 – 13.7% to be exact, with a pretty tight confidence interval. When you look at the perfect use, the people who only correctly and consistently used Phexxi in the trial, the failure rate was less than half that. But that Pearl Index, which is what people may think of as the apples-to-apples comparison between contraceptive methods that the FDA has required for decades, was 27.5. And that Pearl Index is really a strange concept we'll talk more about in a little bit. But that Pearl Index of 27.5 is not that bad, actually; it's actually quite effective. And again, less than 2% of subjects enrolled in the second phase 3 trial discontinued for adverse events, which is huge. As a contraceptive trial, having done many of these as a principal investigator, it's pretty impressive to see a less than 2% discontinuation rate at 6 months.

So this flow diagram shows you how those nearly 3,000 women were screened, and almost 1,400 people were enrolled in the trial. And the reasons for discontinuation are on the right, which we'll dig into a little bit in a minute.

As far as the effectiveness, so over those 6 months, 7 cycles, those nearly 1,400 women, there were over 24,000 acts of vaginal intercourse that were included in the dataset. And what you see here is that failure rate of 13.7% and the confidence interval out to the right. And this is based on a Kaplan-Meier survival analysis. And that's different than the Pearl Index, which is an artificial construct regarding contraceptive effectiveness that we'll talk about at the end.

As I mentioned, contraceptive effectiveness is not just about the mechanisms of action. It's not just about whether someone can correctly use the method, but can they consistently and continually use the method? And a lot of that has to do with do they have side effects, right? So this is a blow up of that table that was in the flow diagram. And what you see is the side effects that people reported in the trial amongst the two phase 3 trials, so there's over 2,400 women in this, and you know, the fact is that while many people describe things like itching or burning or concerns for vaginal discharge or pain with urination, most people who had those symptoms did not discontinue. Again, only 1.6% of participants discontinued due to adverse events, with the most common listed here at less than 1% of discontinuers reporting vulvovaginal burning, for instance.

I will point out, when the FDA took note of this, that the concern for patients who have a high risk of urinary tract infection, and specifically, maybe some urinary tract abnormalities that put them at risk or personal history is someone you might want to consider not using Phexxi for because of the way in which that might increase the risk of urinary tract infection. The numbers were small, however.

And when you think about the fact that this is a contraceptive method that 2 people, the male participant and the female participant in the trial, were asked about their continuation, their satisfaction, and their side effects, a little less than 10% of the male subjects of the female women enrolled in the trial reported some discomfort. And you can see the majority of that was mild, and really only 2 participants in the trial discontinued because of their male partner's complaint of penile symptoms.

So again, you have a high rate of continuation, which translates to a high rate of satisfaction. And we saw that in this second phase 3 trial, not only increasing satisfaction with the method, but increasing sexual satisfaction and function after the first couple cycles. And what you're looking at is people who are very or somewhat satisfied with this contraceptive method, and the percent on the y-axis and each visit across the x-axis, it increased so that 87% of subjects at the end of the 6-month trial said, hey, you know, this is something I'd like to continue using as a contraceptive method. And more than 9 out of 10 said, I'd recommend this to a friend.

So when you think about the tiers of contraceptive effectiveness, this table or this diagram is something that many of us are familiar with. The WHO, the CDC, Contraceptive Technology has produced many different versions of this, where the top tier are the most effective methods, things like permanent non-reversible birth control, things like long-acting reversible contraceptives. The second tier are hormonal contraceptives, including the pill, the patch, the ring, and the injection. And then the third tier are things that are what you might call coitally dependent. And that's where Phexxi, the vaginal pH modulator, ends up. Things like condoms, diaphragms spermicides, plus or minus using those things together. And that's not a huge surprise. And again, the contraceptive effectiveness for Phexxi is dependent on the person who's using it using it correctly and consistently. And so when you do analyze those correct and consistent users, there is a higher success, lower failure rate, not a huge surprise.

Don't forget, a heterosexual couple, having no contraceptive method for a year, 85 out of 100 people will become pregnant within a year. And with a Phexxi user in the typical use, you could estimate it would be about 13 to 14 out of 100. But in that perfect use, it would be 6 to 7.

So how do we determine contraceptive effectiveness? This, I alluded to before. The Pearl Index is the FDA's attempt at an apples-to-apples comparison between contraceptive methods, where you take the number of pregnancies divided by the number of months or cycles of use of that method times a calendar year's worth of time, 12 months or 13 cycles, and you get this artificial Pearl Index.

It's not one that I use in my everyday practice, because it is an artificial construct – the idea of how many pregnancies happen over how many months or cycles of use, and then calculate it over a year. And that measure of pregnancy per year just doesn't make a lot of sense for a lot of people. And over the last couple decades as different contraceptive trial designs have happened both in the United States and abroad, and ways in which we generalize the population to make it less of an idealized contraceptive trial and more generalizable, we've seen Pearl Indexes go up. And that doesn't really make sense when you account for all the different issues around contraceptive failure rates.

And a big piece of that is how we choose what data we include and what data we don't. And so as you think about the ways in which contraceptive methods have been done over the last few decades, what we know is the more recent trials like the one that I mentioned for Phexxi, the phase 3 trials, or the ones that brought the contraceptive patch, Twirla, or the new ring, Annovera, to market is that the FDA has said we need to stop limiting enrollment by BMI or other factors. We need to make sure these are potentially fertile people. We need to make sure we're only including those method cycles in which heterosexual activity occured and no backup method of contraception was used. Throw out the months in which women were in the trial but they might have used a backup method of contraception, for instance.

We also know that we have more sensitive pregnancy tests and more availability of pregnancy tests. And this has resulted in a higher Pearl Index for methods that were even previously approved at a lower Pearl Index, because the construct of the trial is different. And here's a great example of that.

So what we're looking at is different contraceptive pills that have been used as the control compared to when they were approved. And so on the left-hand side, you're looking at the 3 different contraceptive pills, combination or oral contraceptives here, and the Pearl Index in which they were approved, all less than 1. However, more recent trials, on the right-hand side of this slide, you can see that the Pearl Index was more than 4-fold higher when these FDA-approved contraceptive pills that had a Pearl Index less than 1 were the control in a new experimental contraceptive trial. Why is that? It's the same drug. The FDA approved it that way, right?

Well, because the way in which those more recent trials were done is that pill, that same pill that was approved with a Pearl Index less than 1, had a higher failure rate based on the data set, because we were only including months in which no second contraceptive method was used and throwing out any cycle in which there wasn't active heterosexual activity. No surprise, the Pearl Index creeps up.

And so the prescribing information for recent contraceptive methods, the Pearl Indices for these newer methods that I mentioned, the new progestin-only pill, the new contraceptive patch, the new Annovera ring, and the lowest dose hormonal contraceptive pill on the market you see at the bottom there, all have Pearl Indices that are much above 1. And that's not a surprise, because the way in which these trials were done at a more recent era does account for a higher Pearl Index because the construct of the trial is different.

When you look at the relationship between contraceptives and obesity, while the patch, the Twirla patch, which was the secure patch that you see across the bottom here, did have a higher failure rate for patients with a BMI over 30, it's not significantly different than the previously approved patch, Ortho Evra, or Xulane is the other brand name, and many of the contraceptive pills in this forest plot here. And so I will say that contraceptive effectiveness is not only a measure of how well someone uses it and how it interacts, but also continuation. And so we have to take all those things into account. This contraceptive trial design issue is one that muddies the waters when you're trying to use Pearl Indices to compare one contraceptive method to another.

And it definitely doesn't get any easier when you stratify by different BMI classes. The effectiveness for someone who is normal weight, which is less than a third of the population in the United States, is better for the Twirla patch study when you did that life table Kaplan-Meier survival analysis compared to overweight and obese patients.

Now that being said, something that has a 93% effectiveness for a year's worth of use based on the Kaplan-Meier survival analysis is going to be a tier 2 contraceptive method. And what you see here is a similar Kaplan-Meier survival analysis for Phexxi. And over 7 months, there was a 13% failure rate or pregnancy rate over those 7 cycles. And that is where that contraceptive effectiveness number comes from. And again, the perfect-use failure rate was much lower.

So lastly, the secondary analysis of perfect use did demonstrate that amongst those subjects in this bottom line here that used the method correctly and consistently every time without any protocol violations, the failure rate was less than 7% over those 7 cycles or 6 months. So Phexxi is potentially a tier 2 method for those perfect users and a tier 3 method for those typical users.

I'll leave you with these thoughts. You know, we take care of diverse people who can get pregnant who need contraceptive methods, and we the providers need to be able to give accurate information that makes sense to our patients. We need useful data regarding the risks and the benefits to help patients make an informed choice that they can be successful with their contraceptive method. We need to understand that modern contraceptive trials, the ones done in the last 10 years especially, will change the Pearl Index because of the way in which the data is analyzed.

The most effective method that someone can use as a contraceptive method might not work for them if they choose to discontinue it. The most effective contraceptive is something that someone is happy with, that fits their lifestyle, that doesn't cause them troublesome side effects, that gives them the benefits that they want without too many troublesome problems. So I will say that having more and more choices for our patients, for me, is wonderful. I really appreciate industry working to bring new contraceptive methods to market. And I really appreciate the opportunity from Omnia Education to help talk with you guys about this new contraceptive method and some of the new ones that have come to the US market in the last 12 to 18 months.

Thank you for your time.

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