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Managing Vulvovaginal Candidiasis—Riding the Wave of Therapeutic Change

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Managing Vulvovaginal Candidiasis—Riding the Wave of Therapeutic Change” was presented during Omnia Education’s Women’s Health 2021: Beyond the Annual Visit.

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Dr. Nyirjesy:
Welcome to Omnia Education's Women's Health 2021: Beyond the Annual Visit. Thank you for joining us today. I'm Dr. Paul Nyirjesy, professor of obstetrics and gynecology and co-director of the Jefferson Vulvovaginal Health Center in Philadelphia. And in this presentation today, we're going to be taking a closer look at the diagnosis and management of vulvovaginal candidiasis, or VVC. In terms of our learning objectives, after participating in this educational activity, participants should be better able to describe the symptoms, exam findings, and diagnostic testing for vulvovaginal candidiasis, define the criteria by which VVC infections are categorized as uncomplicated or complicated, and describe the advantages and limitations of existing and novel therapeutic interventions for VVC.

So in terms of the epidemiology of VVC, we know that VVC itself is an extremely common condition. The estimated worldwide prevalence is about 70%. The one question has always been what percent of women have recurrent VVC [RVVC]? The estimate used to be 5% of women have recurrent VVC. That estimate was questioned as being too high in a number of publications. And so there are more formal estimates that were done to look at how frequently RVVC happens. And it turns out that that 5% number was too low. And that the current estimates is that perhaps as many as 10% of women suffer from recurrent VVC. And so there are about 138 million women every year who are affected annually by VVC and about 372 million who are affected by RVVC during their lifetime.

So everybody thinks of VVC as being, oh, just a yeast infection, it’s not a big deal. But if you look at the impact on daily life, VVC in general, but RVVC in particular, have a huge impact on quality of life. And so there are psychological burdens, reduced confidence and self-esteem, depression, stress, anxiety. It's somewhat of a stigmatizing disease even though it's not a sexually transmitted infection. In terms of daily activities, patients sometimes become withdrawn from social events or avoid physical activities. In terms of intimacy, there are interruptions in sexual function, there's an impact on sexual satisfaction, there are concerns about women in their reproductive years, about whether yeast infections will impact both their fertility and their pregnancy. And then in terms of medical care, it's embarrassing to be discussing symptoms all the time. And often, again, it's something that's frequently trivialized by healthcare providers, so they may not grasp how important it is to women who suffer from RVVC.

So the challenges with VVC and RVVC is, first of all, it's really difficult to estimate just from diagnostic codes how common these are. And so most providers just use a general vaginitis code; they don't even use the code for vulvovaginal candidiasis. And there is no ICD-10 code for RVVC, which as we'll get into a little bit later, is something that we should think about in a different way than VVC. I think partly as a result of that, there are issues with under-recognition. We've already talked about a trivialization of the disease. And I think that most providers don't think to differentiate acute episodic VVC from women who are more complicated.

There are also issues with self-treatment. There are studies that show that at least 50% of women who self-treat for VVC don't have a

yeast infection at all. So there's a lot of overuse. And then there's also underused for patients who focus on the wrong symptoms who think that if they're really itchy, it's probably not a yeast infection at all. Whereas it turns out that the main symptoms that yeast infections cause are itching and irritation. And part of the drive towards self-treatment, again, is the discomfort that some women may have in discussing their symptoms.

And then in terms of management for RVVC, I think partly because there are no FDA-approved treatments, I think many providers are unaware of current treatment recommendations. They may not be aware of the limitations of the current treatment options; there aren't very many treatment options. And then there are adverse effects and contraindications to the treatments that are currently available.

And then in terms of outcomes, there are high recurrence rates, even with RVVC that is correctly treated. And we'll be talking about maintenance therapy a little bit later. But there's also often a lack of adherence to maintenance therapy.

So in terms of diagnosing VVC, it's important to realize that there are different modalities for testing are currently available and that they are frequently used inappropriately or misinterpreted. And so the standard for many people is to use microscopy. The advantage is that it's cheap; you get results immediately. But the sensitivity is not as good as people may think when it comes to yeast infections. And it's been estimated that the sensitivity is about 40% to 70%. And then there are also issues with overdiagnosis, depending on the provider, and then with the sensitivity of 40% to 70%, issues with underdiagnosis if a provider is just relying on microscopy. So culture is what's recommended when microscopy is negative and women are symptomatic. And I tend to do cultures even if the pH is abnormal, but certainly if somebody is symptomatic and has a normal pH and doesn't have bacterial vaginosis, culture for yeast should be recommended. The disadvantage of cultures is that it may take days to weeks. The advantage is that it identifies the species of yeast, which is causing the symptoms, which is really important. It may be limited if the patient comes in and she's partially treated because that can turn a positive culture to negative just from the treatment she's taken. But it's certainly recommended to do cultures in patients where they have resistant yeast. You can also do resistance testing if you're suspecting it, also somebody with recurrent or refractory disease. And it's also important to understand that doing a yeast culture is the current gold standard for diagnosing yeast infections.

So it turns out that most providers don't do yeast cultures, which is a shame; it's really easy to do. Turns out that maybe 5% of providers consider doing yeast cultures. And to fill the gap, what's now become actually very popular is DNA probe and PCR testing for yeast infections. So the DNA probe, some of you may be familiar with, it is the vaginitis panel. The advantage of it is that you get results within hours, but it's actually not that sensitive. The sensitivity of the DNA probe is about 50% to 60%. So now there are nucleic acid amplification tests are available; some of them are FDA cleared. They're available in many commercial labs. And it really is a good test for *Candida albicans* infections, which are the most common cause of yeast infections. But they may not be as good for the non-albicans species. And this is part of the reason why doing yeast cultures is still considered the gold standard for diagnosing yeast infections.

So let's turn now and talk a little bit about pathophysiology. So for a woman to get a yeast infection, the process starts with yeast getting into the vagina and the woman being colonized with yeast. And so there are probably various sources for where yeast comes from. It's a really common question I get in my practice, you know, why am I getting yeast? Where's it coming from? And the bottom line is that it might come from the GI tract; it might come from sexual activity; it might come from all sorts of environmental exposures. But most women who get yeast in their vagina are completely asymptomatic from it. They're just asymptomatically colonized; it doesn't need to be treated if they're asymptomatic. And this is a really common life event for almost every woman.

But then what happens is, in some women, they go from being asymptomatically colonized to being symptomatically infected, and why that happens isn't clear. In some women, there may be a genetic predisposition or there may be some sort of trigger that causes an overgrowth of yeast. The common triggers that we think of would be, for example, diabetes, antibiotic use, in a woman who is menopausal, taking estrogen therapy. But so what happens is she goes from being asymptomatically colonized to being symptomatically infected. In those women if it's just a sporadic episode, you can give them an acute treatment for 1 to 7 days. But then what seems to happen in recurrent yeast infections is that there's something underlying about the woman with RVVC, probably a genetic factor, where the response that her vagina specifically has to the yeast lays the groundwork for the next infection. And so she gets into this pattern of infection, kind of getting better with treatment, a relapse of the infection, kind of getting better with treatment, but the process just keeps going and going and going. And so in those women, and again, we'll talk about this in more detail, the only approach to treatment that seems to be helpful is putting them on maintenance therapy. If it's *Candida albicans* infections, we treat them with a long course of fluconazole which works quite well at controlling the symptoms. But then within 6 months of stopping treatment, the yeast infections come right back.

So during these introductory comments, I've talked about sporadic VVC and recurrent VVC. And in terms of treatment, it's really important to differentiate between the two and also just understand the differences. So sporadic, by definition they're infrequent episodes. Often patients will have identifiable triggers, and we already talked about those. And so sometimes avoiding those triggers may be helpful. There are loads of different treatments that are approved for sporadic VVC ranging in duration from 1 day to 7 days.

And for most patients who have sporadic VVC, they'll get better with pretty much anything that you give them.

But then for women with recurrent yeasts, I think it's helpful to think of it more as a chronic disease. The current definition is 3 or more episodes a year. In terms of the triggers, patients may have similar triggers to the sporadic patients. But at least 50% of women with recurrent VVC have absolutely no identifiable triggers. As I've mentioned already, there are no FDA-approved treatments. They should be treated long term. And for most patients, you can at least get a resolution of acute symptoms, but then once you stop treatment, those patients will recur.

And so what are the current treatment modalities? So for acute VVC, there's miconazole, terconazole, clotrimazole, tioconazole, butoconazole. They're all topical agents that are available in different formulations. There's creams; there's suppositories. They all work about the same for an uncomplicated *Candida albicans* infection. There's oral fluconazole single-dose 150-milligram pills. And then just recently approved by the FDA in June 2021 is ibrexafungerp, which is a drug I'll be talking about in more detail a little bit later which is now another FDA-approved treatment for acute VVC.

So when selecting therapy, what the CDC guidelines have mentioned, probably since the 2010 guidelines – so for at least a decade, and it might have actually been in the ones that were created, I think it was 2005 or 2006, so the ones that were before then – is that we should be differentiating between uncomplicated candidiasis and complicated candidiasis.

So women with uncomplicated candidiasis have infrequent episodes, sporadic episodes. Usually it's a *Candida albicans* infection. They have mild to moderate symptoms; they're immunocompetent. Again, those are the women where any of the FDA-approved regimens are going to work. Then there are the complicated women who have a non-albicans infection. Somebody has a really severe infection, she's actually considered complicated. And there are actually scoring systems to help you decide is she severe, is she not severe. I would make it easy. If she tells you she's really itchy, she's probably got a severe yeast infection, or if you look and you think she's really red and swollen, right away she would score into the severe category. And severe infections don't respond to the single dose or the uncomplicated regimens that are currently available. Recurrent is now defined as three or more a year. And then the other patients who fall into the complicated criteria are women with uncontrolled diabetes. HIV is actually listed in there, although it's not clear that HIV-positive women are really more complicated. But immunosuppressed – those women who are immunosuppressed for other reasons, like on prednisone for arthritis or something of that sort, they're definitely more complicated and won't respond to standard treatment as easily as other women.

So the guidelines for treatment of the VVC they depend a little bit on which organization you look at. But in general, for uncomplicated you can give them a topical agent for 1 to 5 days, or even 1 to 7 days, or give them a single dose of fluconazole. For complicated, consider initially treating them for somewhat longer course of therapy, 5 to 7 days or 7 to 14 days or 10 to 14, days depending on the organization, with topical agents. But really what they should do is go on maintenance therapy. Fluconazole 150 milligrams every 72 hours times 3 doses initially followed by once-a-week fluconazole for 6 months. And the regimen, by the way, that I use a little bit different, I use 200-milligram pills. And the reason is that some insurance companies won't let patients have more than one or two 150 pills a month. They'll actually let patients have as many 200-milligram pills a month as you want. And 200 milligrams once a week is quite effective. And so we use that dose, not to give a higher dose but just to get it into a patient's hands more easily.

So fluconazole has been around since 1990 – or I think it was approved as a drug in 1989. I've been using it for RVVC since 1992. It's been a big step forward in helping women with recurrent VVC. It is not a cure-all. So from the very beginning, it was very clear that fluconazole does not work very well for non-albicans species, particularly *Candida glabrata*, which is the second leading cause of yeast infections. More recently, and probably because fluconazole has now been around for decades, there are more and more reports of *Candida albicans* infections that are resistant to fluconazole. And those patients are a real struggle. We have probably a new patient with a resistant *Candida albicans* infection in our practice every couple of weeks. So these are really patients who suffer quite a bit.

In terms of tolerability, sometimes it can cause alopecia. People always talk about liver and cardiac toxicities, which are actually fairly rare. But you do need to be aware about drug-drug interactions.

And then the biggest issue, which is really only been highlighted in the last 6, 7 years, is that it's associated with a potentially increased risk of miscarriage if given even right before conception. And there's also a question about whether or not it may be associated with cardiac defects. And I know that many providers use fluconazole in pregnancy. Technically, it's contraindicated in all trimesters of pregnancy. And I do not use fluconazole in somebody who's pregnant or who is actively trying to get pregnant.

And then the other challenge is that even in the patients to do really well with maintenance therapy, they may recur after they discontinue maintenance.

And so with that, what I'd like to do is I'd like to talk about two new drugs that I think are worthy of focus. One of them which was recently approved, ibrexafungerp. And then later on, we'll talk about oteseconazole.

So ibrexafungerp was approved by the FDA on June 2, 2021, as the first and only oral non-azole treatment for vaginal yeast infections. It's a first-in-class triterpenoid. And it – unlike the azoles that all attack the cell membrane, this attacks that glucan synthase inhibitor in the cell wall. There's some overlap with the binding site of echinocandins. It's very specific, so there are fewer drug-to-drug interactions than with fluconazole. It's quite bioavailable, has a nice half-life, 20 to 30 hours. And what's very important is that unlike echinocandins, you get very high levels of penetration into the vaginal tissues with a 1:9 plasma to vaginal tissue concentration. Ibrexafungerp cleared the phase 2 trials for acute VVC. They're now phase 3 trials. Some of them completed, some of them ongoing for both VVC and RVVC.

So if we compare ibrexafungerp to fluconazole, we have a new drug that has a novel mechanism of action that acts against the cell wall instead of the cell membrane. This is a drug that is thought to be fungicidal as opposed to fluconazole, which is fungistatic. In vitro, it's very active against azole-resistant species. Keep in mind that the pH of the vagina is low, and ibrexafungerp does not seem to be affected in its activity by low vaginal pH. It turns out that some yeasts that look great with fluconazole at physiologic pH, actually seem to be very resistant to fluconazole at a lower pH. We already talked about the really good vaginal tissue penetrations. There's no evidence of fetal toxicity, whereas with fluconazole, now there is. With fluconazole, there are concerns about QTC prolongation, which is not an issue with ibrexafungerp. There's no evidence of liver toxicity. And then similar to fluconazole, it's approved as a single-day dosing.

And so some of the data comes from studies such as this one, the phase 2b DOVE study which was a randomized, multicenter, double-blind, active-control, dose-finding study which was the first study to look at the efficacy and tolerability of oral ibrexafungerp versus fluconazole. And I think it's worth stressing that this is really more of a small study as part of a dose-ranging study and kind of the first look at efficacy. They looked at women with moderate to severe acute VVC. The primary goal was to look at clinical cure, and they found that the drug was generally safe and well tolerated. There are no serious adverse events or discontinuations. The main issue may be some mild GI events, nausea, diarrhea, abdominal pain. And if you look at the cure rates compared to a single dose of fluconazole, you had similar cure rates at day 10 and day 25. Keep in mind, by the way that ibrexafungerp is one-day dosing, but it's 300 milligrams twice a day.

So since then, ibrexafungerp has gone on for the phase 3 trials for acute VVC, the VANISH-303 and the VANISH-306 studies. Both of them were identical randomized, multicenter, double-blind, placebo-controlled studies of women aged more than 12 years. And so the way the study was set up is that patients came in for the screening, and then 188 patients were randomized to ibrexafungerp versus 98 who randomized to placebo. And then patients came back for a test of cure. And by definition it was decided that only the modified intent-to-treat population would be studied in the analysis of patients who had a positive culture at baseline when they were enrolled. And so the primary endpoint was a percentage of subjects with a clinical cure, complete resolution of signs and symptoms at the test-of-cure visit. Other secondary endpoints were the ones that you would think of makes sense. Looking at what happens to the yeast culture and how many of those yeast cultures turn negative at the test-of-cure visit and also looking at the percentage of patients who maybe didn't have complete resolutions of signs and symptoms but felt a lot better. And then also looking at the patients who still had a complete resolution of symptoms at day 25. And then the study also looked at safety and tolerability.

So in terms of the demographics, the ibrexafungerp group and the placebo group were pretty well matched. Over 90% of all of these women had *Candida albicans* infections, which is what you'd expect in the general population. And so overall, the two groups were really well matched about what you'd expect for a study of VVC.

Looking at the efficacy endpoints with clinical cure at the test-of-cure visit, 50% of the ibrexafungerp patients versus 28% of the placebo patients were clinically cured. With mycological eradication, it was 49.5% versus 19.4%. Clinical improvement 64.4% versus 36.7%. And symptom resolution at follow-up, 59.6 versus 44.9. Which just shows that there was a really nice, sustained response to therapy which actually went well beyond the initial test-of-cure visit. And all of these numbers, by the way, were statistically much better than the placebo group and statistically significant.

So in terms of safety there were about 185 patients in the ibrexafungerp versus 76 patients in the placebo group who had some sort of therapeutic AE. If you look at the overall AEs, they were similar across both groups, except for diarrhea and nausea, which seemed to occur a little bit more often in the ibrexafungerp group versus the placebo group. Also abdominal pain. So there may be some GI symptoms. Most of those patients who had the GI symptoms, they were mild.

So then there's oteseconazole. So this drug is still considered investigational. The FDA has accepted the priority review of the new drug application for oteseconazole for the treatment of recurrent vulvovaginal candidiasis. The target for approval is going to be early 2022 pending full FDA approval later on.

So with oteseconazole, this is a drug that is similar to fluconazole but has a more specific action against ergosterol synthesis. So again, it's working on the cell membrane. It seems to have a more specific action and fewer drug-to-drug interactions. And the first paper that was published was a phase 2b dose-ranging study, a randomized, multicenter, double blind, placebo-controlled study, and there were 176 women aged 18 to 64 years of age who completed the trial. And they all had RVVC. They were treated initially with 3 pills of

fluconazole, 3 days apart to treat the initial infection. And then they were randomized to 4 different dosing regimens of oteseconazole or placebo.

And so in the results, which were published a few years back in the *American Journal of Obstetrics and Gynecology* what we find in this graph is that in the blue line that goes all the way down, the light blue solid line, that's the placebo group. And so during this study, about half of the patients who got placebo after clearing the initial infection recurred. And if you look at the groups that got oteseconazole, no matter what the dose, the groups had an extremely low recurrence rate and they actually were not able to calculate a median time to recurrence with the oteseconazole group because there are so few recurrences. With the placebo group, it was 28 weeks median time to first recurrence.

So in terms of safety outcomes, most of the adverse events that occurred after treatment were thought to be unrelated to the study drug. Things like urinary tract infection, bacterial vaginosis, sinusitis, headaches, upper respiratory tract infection, and nausea. And there were no drug-related serious adverse events in any treatment arm.

So there are more studies ongoing with both of these drugs. With ibrexafungerp, I already shared the results from the 303 study. There's also a 306 study that's been completed. And both of those papers are going to need to be fully published and reviewed. Then there's a trial going on with ibrexafungerp, looking at RVVC, where patients get fluconazole 150 milligrams every 72 hours times 3 doses. And then every 4 weeks, they get either a day's worth of ibrexafungerp versus a matched placebo. And then similar to other maintenance studies, patients will be followed during the 24 weeks of treatment and also the 6 months after that. That study, my understanding of it is that it's very close to completion. I do know that enrollment is closed on this study, and now it's just a question of getting the patients to complete the study.

So with oteseconazole, it's now been undergoing what's known as the VIOLET study. This is a phase 3 study. The results were actually presented in early August as an abstract at the IDSOG 2021 meeting by Jack Sobel. It's the results from 2 parallel randomized, multicenter, double blind, placebo-controlled studies. Similar to the ibrexafungerp study and other maintenance studies, patients got 3 doses of fluconazole 3 days apart, and then they were randomized to 3 months of treatment with oteseconazole versus a placebo. And the total study period was 48 weeks. There were more than 600 women enrolled in this very large study of RVVC. And what was presented at this meeting was that oteseconazole protected more than 90% of participants from a recurrence during the 48-week maintenance and follow-up phases compared to only 40% in the control group. Oteseconazole was generally safe and well tolerated with no drug-related severe adverse events reported. And the study investigators concluded that oteseconazole oral dosing was effective in the treatment of RVVC and the prevention of recurrence of acute VVC episodes during maintenance through week 48.

So oteseconazole, again, they're doing more studies – the ULTRAVIOLET studies where they they're comparing oteseconazole to fluconazole for both acute and maintenance treatments. And so instead of using fluconazole to get rid of the initial infection, they're going to be using oteseconazole to get rid of the initial infection. And then patients will get randomized to once-a-week oteseconazole versus once-a-week fluconazole.

And so with both ibrexafungerp and oteseconazole, there are clear advantages over fluconazole. There are longer half-lives; there are high tissue concentrations in the vaginal tissue. Both drugs seem to have less potential for drug-to-drug interactions. Both drugs seem to be very effective in vitro against the strains of yeast that are resistant to fluconazole. And with the initial data that we have there seem to be higher numbers of recurrence-free rates versus fluconazole. But we still really need to wait for the results of more phase 3 trials and acute VVC and RVVC.

In closing, I just wanted to kind of emphasize, first of all, that RVVC is not a trivial disease. The mainstay of treatment, maintenance fluconazole, has been the same for about 30 years. So there's clearly been a need for something new to come along, and I've seen drugs come and go during that 30 years. But both ibrexafungerp and oteseconazole have unique qualities that I think lend themselves really well to the treatment of VVC. And I think that initial data suggests that both may represent a significant step forward in managing a challenging infection.

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