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### Innovations in the Management of Dyspareunia

Voiceover:

Welcome to CME on ReachMD. This activity, titled "Innovations in the Management of Dyspareunia" is provided by Omnia Education. This activity is supported by an independent educational grant from AMAG Pharmaceuticals.

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Your host is Dr. Renée Allen.

Dr. Allen:

Vulvar vaginal atrophy, or VVA, affects about half of the 64 million postmenopausal women in the United States. VVA stems to the loss of estrogen stimulation on vaginal and vulvar tissue, which can lead to symptoms of dyspareunia or painful sexual intercourse. This, in turn, can negatively impact sexual function and sexual relationships reducing overall quality of life. This is CME on ReachMD, and I am Dr. Renee Allen. Joining me to focus on the diagnosis of dyspareunia associated with VVA, and therapies indicated for the management of this condition, is Dr. David Portman, Director Emeritus at the Columbus Center for Women's Health Research and Adjunct Instructor of Obstetrics and Gynecology at the Ohio State University in Columbus, Ohio.

Dr. Portman, welcome to the program.

Dr. Portman:

Thank you Dr. Allen. It is great to be with you.

Dr. Allen:

Wonderful. Dr. Portman, let's start by reviewing the key components in diagnosing dyspareunia associated with vulvar vaginal atrophy.

Dr. Portman:

Well, dyspareunia associated with VVA, for short, vulvar vaginal atrophy, is a clinical diagnosis and it is a very common condition. As you mentioned, upwards of 50% of postmenopausal women are affected by painful intercourse. However, VVA also encompasses other symptoms, other common symptoms, such as dryness, burning, irritation and other symptoms associated with genital and urinary tract symptoms. In fact, we've recently grouped many of those symptoms into a syndrome called Genitourinary Syndrome of Menopause, of which symptomatic VVA is a component. So in a woman, postmenopausal, comes in with newly diagnosed painful intercourse, she certainly has a symptoms of VVA and you exclude other possibilities, but in all likelihood, those common symptoms are very obvious to both the patient and the clinician. One of the biggest challenges is getting the clinician to be aware of the condition, talk about sexual activity with their midlife patients, as well as make sure the patients are comfortable bringing this up as a significant quality of life issue.

Dr. Allen:

What about perimenopausal and menopausal women who don't report symptoms, Dr. Portman. Should they also be evaluated for dyspareunia associated with VVA?

Dr. Portman:

I think one should ask all of the patients who are in that menopausal transition, which is typically 47 to 52, about any new onset symptoms. Women are very aware that hot flashes, probably one of the most common symptoms of menopause, occur during that change. However, because the onset of vulvar vaginal symptoms such as dyspareunia pain can be gradual and happen either before or after hot flashes have occurred, it is very important to evaluate all women as they both transition through midlife as well as beyond. Many women continue to remain sexually active postmenopausally, and surveys show that it continues to be very important to them, and clinicians the more awareness they can have, are likely to help patients who may go undiagnosed otherwise.

Dr. Allen:

Dr. Portman, can you help us understand the pathophysiology underlying VVA in more detail and how this presents clinically?

Dr. Portman:

Yes, so the estrogen and androgen receptors are probably found at their greatest density in the urogenital tract. That's why it is exquisitely responsive to the hormone changes during reproductive years to create menstruation. Those same hormones, primarily estrogen in the premenopause made by the ovary, continue to maintain vaginal health as well as vulvar health, as well as androgen receptors found very commonly in the vulva as well. With menopause the decline in those sex steroids leads to changes often rapid and insidious in some patients and gradual in others, where the tissue gets dry, the epithelium gets fragile and can be injured or bleed with very little contact or trauma. Symptoms can also affect the lower urinary tract and cause symptoms such as dysuria as the urethra can be significantly affected by these changes as well. If it goes untreated, those tissues become less and less elastic, can't stretch to accommodate penetration and, ultimately, can become so stenotic that intercourse becomes impossible.

Dr. Allen:

Dr. Portman, when thinking about a diagnosis of vulvar vaginal atrophy, what are the conditions that should be considered and what are the conditions that should be ruled out?

Dr. Portman:

It is one of the most common causes of dyspareunia or some of the other symptoms that we describe such as dryness, irritation, burning, sometimes discharge. Those can also be symptoms of common vaginal infections. Postmenopausal women can get candida as well as bacterial vaginosis infections. Those should be treated appropriately. It doesn't mean that VVA doesn't coexist with those conditions. We also want to rule out any significant vulvar pathology. Make sure that there is no dermatosis there, such as lichen sclerosus or lichen planus. Those are several common dermatoses that we encounter in gynecology that can often be misdiagnosed. Patients could have vulvodynia, and that is not necessarily associated with vulva vaginal atrophy, but may be neuropathic in origin. And, certainly, any lesion or color changes should be evaluated to rule out a malignancy or a dysplasia.

Dr. Allen:

If you are just joining us, this is CME on ReachMD, and I am Dr. Renee Allen. Joining me today is Dr. David Portman, and we are discussing diagnostic and treatment options for dyspareunia. In assessing treatment options, Dr. Portman, the FDA identified four co-primary endpoints that must demonstrate significant improvement. Can you elaborate? What are these endpoints?

Dr. Portman:

While we, in clinical practice, look to patients to report those symptoms and identify the appearance of vulva vaginal atrophy, there are set guidelines from the FDA in order to get products approved for the treatment of symptoms due to VVA. There are three objective parameters. Some of these are looked at clinically by some doctors and practitioners in the office, others it's used solely as research tool, and those are vaginal pH, parabasal, and superficial cells. The healthy vaginal epithelium has a thick superficial layer that helps protect the vagina from injury. It also is replete with glycogen which is metabolized into lactic acid and has increase of the vaginal pH when there are changes to be more alkaline. The healthy vagina has a low pH; in menopause that increases, and you see these immature parabasal cells. So, those three parameters are looked at to improve with treatments, so you want to make sure that you see the pH move in the right direction with treatment and you want to see an improvement in superficial cells and less parabasal cells. You also want to make sure that the patient has a moderate to severe symptom. The most common symptoms are usually dyspareunia or vaginal dryness and the FDA has suggested that you study those symptoms separately, although, in clinical practice, there may be significant overlap.

Dr. Allen:

What therapies, then, Dr. Portman, have been approved by the FDA for the management of VVA-associated dyspareunia?

Dr. Portman:

Well, we've had local vaginal therapies available to us for decades. And, in fact, up until the recent guidance from the FDA, many of those therapies were approved based on simply changing some of the parameters that we described, such as pH, or various symptoms. They didn't use what they now refer to as the most bothersome symptom, where the patient picks one specific symptom, and that has to

improve with treatment. So, vaginal creams, tablets, and rings have all been available, some brand products, others generic, to treat the symptoms locally. They each have their pros and cons. The creams can be messy. Some women don't like the use of a ring which may fall out or may be uncomfortable with intercourse. They also have significant concerns about the box warnings that are associated with these products. And while the data on safety with low-dose vaginal estrogen does appear different and likely safer than systemic estrogens, the FDA still mandates a class label which identifies cardiovascular risks, endometrial cancer risks and even dementia as potential risks. So, that often frightens patients and they may discontinue a treatment that is working quite well for them.

The newer treatments approved have been largely approved for one symptom of vulva vaginal atrophy and that has been dyspareunia most recently, with drugs approved within the last several years for that symptom associated with VVA.

Dr. Allen:

Dr. Portman, as clinicians and also specifically as OB/GYNs, we know that estrogen therapy has been available for many decades, but can you tell the listening audience, what's currently known about its benefits and its drawbacks?

Dr. Portman:

Well, I think that we covered some of those with the previous question, but the biggest challenge really is in counseling and awareness of benefits and risks, and in this day and age, still decades after the Women's Health Initiative, which identified that estrogen therapy may not have all the benefits that we had thought it had, there is still a lot of fears of estrogen and patients don't understand the difference between local and systemic administration. Some of the challenges with low-dose vaginal estrogen tablets can often be that they don't treat the outer part of the vagina or the more distal part, given that the tablet stays high in the vagina and the outer lips of the labia often go unaddressed, and also have lots of androgen receptors, which may need a different approach to treatment.

Dr. Allen:

In the past few years, Dr. Portman, several non-estrogen products have been approved by the FDA for dyspareunia associated with VVA. One of these is the oral selective estrogen receptor modulator, ospemifene. Can you discuss its benefits, and its limitations?

Dr. Portman:

So, I was one of the lead investigators and author of the ospemifene trials. So, I can certainly give you a very high level overview of what we found in the clinical study and that ospemifene, which is in a class of drugs called a SERM, or a selective estrogen receptor modulator, in early animal studies showed that it had benefits on vaginal tissue as well as on bone and breast tissue, but it ultimately was investigated as a drug for vaginal atrophy and improves all the parameters that we had discussed. It can lower the pH and improve superficial and parabasal cell counts, and it also improved the patient's most bothersome symptom of dyspareunia. One of the challenges with a drug that you take orally is that it gets to other tissues and the warnings regarding its effect, either known or suspected, can often be a deterrent in patients' acceptance. So, for instance, it too carries a boxed warning for endometrial stimulation and potential cancer, however, that hasn't been borne out in clinical studies, but it is still a theoretical concern, and many women may want a local therapy, rather than taking a pill that gets to all the body and all the systems. However, many women also like the convenience of daily oral tablets. So, the patient usually makes a decision with her clinician based on what's right for her and the balance of benefits and risks.

Dr. Allen:

There is an additional new agent named prasterone, that is an inactive endogenous steroid. And it's converted locally in the vagina into androgens and estrogens. Can you, then, Dr. Portman, describe its respective benefits and its limitations as well to us?

Dr. Portman:

Sure, I was also an investigator and author of the prasterone trials, and it's nice to see clinical studies that we conducted, and all the patients that helped and volunteered to finally these various options available. Like ospemifene, prasterone or intravaginal DHEA was approved for the treatment of moderate to severe dyspareunia symptom of vulva vaginal atrophy in that the patients presented with that as their most bothersome moderate to severe symptom. The drug is administered intravaginally as a suppository with an applicator nightly. So it is part of their nightly routine. And what's very interesting about this particular therapy, is that it acts as a prodrug and that DHEA, which is the active ingredient of prasterone, is converted intracellularly to estrogens and testosterone in the vagina and the vulva. We've often forgotten that there is a lot of sex steroids that are made because of this type of peripheral conversion with adrenal production of DHEA, and when menopause occurs both estrogen drops precipitously from the ovary, but also, you have a loss of estrogen and androgens locally because there is less DHEA. So, prasterone is a supplement to the vaginal tissue which is converted into estrogens and androgens and it improved all the parameters of vulva vaginal atrophy. In the clinical trial you saw a decrease in the patient's pH and improvement in superficial and parabasal cells as well as an improvement of their most bothersome symptom of dyspareunia. So, it too, is a new option and alternative to estrogen, and the label is much different and the counseling is much different than both ospemifene and local or systemic estrogens, and that there is no boxed warning. That was largely due to the fact that in a

study that I published on the endometrial effects of prasterone, that there was no stimulation of the endometrium. This may be because in a normal endometrium they haven't found the enzyme aromatase, which would be necessary to convert DHEA into estrogen in the endometrium. So, it appeared very safe on the endometrium. There were no cardiovascular warnings as well. The only abnormality that was seen was an increase in abnormal PAP smear at the end of the study, which showed about a 2% rate of abnormal PAPs, which is pretty similar to what we see in the general postmenopausal patient population and that may be an incidental finding. There is also vaginal discharge as a side effect that was reported. But, otherwise, counseling for patients who see this as an option is pretty straightforward and the label allows them to take this nightly with pretty significant confidence. Again, patient preference for vaginal versus oral route of administration may come into play, as well as the other tissue effect that the options such as estrogens and ospemifene offer. So, it's nice now that patients have a variety of treatments and it's not one-size-fits-all.

Dr. Allen:

Dr. Portman, as we are nearing the end of the CME, do you have any final thoughts for our listening audience?

Dr. Portman:

I think that the most important thing to remember is, if you don't ask or look into this condition, it will often go undiagnosed and untreated. Starting that conversation, evaluating all patients who are peri- and postmenopausal to see if they do have signs and symptoms of VVA, especially the very bothersome symptom of dyspareunia, which, as you mentioned, can interfere with intimacy and relationships and self-esteem, and there are so many options out there that it really is a shame that patients and clinicians don't take advantage of the opportunity to treat a relatively simple to treat condition and, hopefully, with that growing awareness and with those options, will have much greater patient satisfaction in the future.

Dr. Allen:

Well, with that, I want to very much thank Dr. David Portman, for speaking with me about the diagnosis and management of dyspareunia and the treatment options that are now available.

Dr. Portman, it was great having you on the program. Thank you so much.

Dr. Portman:

Thanks for having me today.

Voiceover:

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