Transcript Details

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EndoShare 2022: A Patient-Centered, Evidence-Based Approach to Managing Endometriosis Pain

Announcer:
Welcome to CME on ReachMD. This activity entitled "Endoshare 2022: A Patient-Centered, Evidence-Based Approach to Managing Endometriosis Pain" was presented during Omnia Education's Women's Health 2022, Beyond the Annual Visit.

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

Dr. Taylor:
Hello. I'm Dr. Hugh Taylor. I'm Professor and Chair of the Department of Obstetrics, Gynecology and Reproductive Sciences at the Yale School of Medicine. I'm here today to talk to you about endometriosis. In particular, we're going to talk about a patient-centered, evidence-based approach to managing endometriosis pain. My conflicts of interest are disclosed here. My university received a grant to support my research.

The learning objectives of this presentation are stated here. We will identify clinical practices to support the accurate and timely diagnosis of endometriosis, we will assess the benefits and challenges of various medical therapies for initial and ongoing care of women with endometriosis, and we will evaluate recent clinical trial and real world data about medical management of endometriosis.

I think most of you know that endometriosis is a complex gynecologic condition that can cause severe pain and/or infertility. Many women suffer from this disease for many years, and the symptoms are unfortunately sometimes just dismissed as normal. Pelvic pain, dysmenorrhea sometimes can be easily dismissed. Menstrual pain is the only pain that we as human beings accept as normal, and it's very hard to judge if your pain is worse than someone else's. Also, there's tremendous lack of awareness of this disease, that results in delays in recognition, diagnosis and treatment, and leads to poor outcomes and decreased quality of life. And finally, there is some stigma surrounding menstruation that compounds the burdens of the disease – it makes it harder to discuss.

Endometriosis is defined as ectopic endometrial glands and stroma. Histology is shown in the figure in the upper left. It's thought to arise through retrograde menstruation, in other words, menstrual flow backwards out the fallopian tube, where it implants in the dependent areas of the pelvis. But I think this simple definition belies the complexity of the disease. Even the appearance can be quite varied. Sometimes we see the classic blue lesions in the pelvis, sometimes we see brown lesions, black lesions, white-looking lesions, or even the more subtle clear vesicular lesions, and sometimes we see the large endometriomas – the cystic structures in the ovary. So it really can be quite different in its appearance.

Not only that but the clinical presentation can be quite variable as well. Sometimes we see patients with extreme pain. Sometimes they have no pain whatsoever, and we don't see them until they come in because they can't get pregnant, with infertility. And sometimes they have absolutely no symptoms – they were able to get pregnant, they don't have pain, and we find it incidentally when we're doing some other type of scan or perhaps surgery for another indication. So again, this is a complex disease. And even when someone has pain, the pain that we see is not related to the stage of the disease. Whether we look at dysmenorrhea or non-menstrual pelvic pain, or dyspareunia – painful intercourse, the amount of pain someone has is the same no matter whether they have stage 1 disease or stage 4

disease.

So, again, this isn't just about the blue dots that we see in the pelvis. It's much more complex. What you see in the pelvis is not the whole story. It affects multiple aspects of our physiology and areas throughout the body. Not only do people have those painful symptoms from endometriosis in the pelvis, they may have infertility as we discussed, but they also have a higher incidence of affective disorders such as depression or anxiety. We know that they have whole body inflammation that often leads to fatigue. They can have bladder dysfunction, they can have bowel dysfunction, and now we're starting to learn that there may be long-term consequences to endometriosis, such as an increased risk of cardiovascular disease later in life. This really is a much more complex disease than just those few blue dots in the pelvis.

It really is a systemic disease that affects the whole body, and what we have referenced here is a paper we published around November of last year. It tries to shift this paradigm of thinking of endometriosis as just a few lesions in the pelvis, to thinking about this as a chronic, systemic disease that affects the whole body. Some of our research has confirmed this. We've done animal studies where we can really determine cause and effect. We can create endometriosis in mice and have carefully selected controls, where everything's the same, including the same genetic background. But just look at the effect of the endometriosis, and indeed, we show endometriosis causes inflammation, endometriosis causes weight loss. We've often heard it reported incorrectly, and it's still in a lot of textbooks, that being thin is a risk factor for endometriosis. Well, our animal experiments show us it's exactly the opposite – the cause and effect is reversed – that when you create endometriosis, you lose weight, you lose body fat. Endometriosis changes our metabolism, and we found effects in the liver and an adipose issue that regulate this change in metabolism, leading to decreased body weight.

We also see a direct effect of endometriosis on the brain. Again creating endometriosis in animal models makes those animals develop anxiety, depression, and makes them more sensitive to painful stimuli. They have central pain sensitization. It is not that endometriosis patients are depressed or anxious and complain more about the pain – no. The endometriosis causes these symptoms.

The anxiety and depression is a consequence of endometriosis, and part of the disease. We need to recognize this. And again, as I mentioned earlier, we see women with endometriosis, in the long run are starting to show increased risk of various cardiovascular diseases.

And I want to show you this, in the next slide is our animal model. We've just recently published this, so I wanted to put this data up. Many of you probably haven't seen this as of yet. Here we use a mouse model – a mouse that has an incidence of endome – rather of atherosclerosis that's similar to humans. Most mice don't get much atherosclerosis, but this is a mouse model where they develop atherosclerosis similar to humans. And when we create endometriosis in these mice, we start to see their red plaques – the atnerosclerotic plaques that are forming in those aortas, shown to the left. You can see that the amount of that red oil that's taken up by fatty lesions is increased. You can start to see that the vessel wall is thickened, so the lumen becomes contracted and smaller. The vessel wall is thickened as these mice develop endometriosis-related atherosclerosis. This is cause and effect. The controls don't get it, whereas those with endometriosis get it as a consequence of the endometriosis.

So, endometriosis really has quite a bit of varied effects in the body. What we're seeing is really just the tip of the iceberg. When we talk about the pelvic pain, the lesions in the pelvis, it's not really taking into account the total effect of endometriosis on a woman's health and on a woman's life. This is reflected in some of the surveys that we see done that women with endometriosis perceive multiple different effects on their lives. They perceive a change in appearance. They think that no one understands them. They see mood changes. They feel that the pain controls their life, that the pain may interfere with their work or their daily activities. You can see from these statistics, about two-thirds of women report moderate or extreme loss of productivity. And nearly all of them – over 80% here – report changes to their daily life or activities. This is a disease with profound effect, largely pain-driven, but many of these other symptoms come from all of those other systemic aspects of endometriosis.

I think this has led to challenges in diagnosing endometriosis traditionally. We know from many studies that it's an average of 6-11 years from the first onset of symptoms – classic endometriosis symptoms – until we make a definitive diagnosis and treatment. We can do better than this. What are some of the reasons for this? Well, I think many of us – patients and even medical providers – are not familiar with this disease. We also mentioned earlier that social norms sometimes inhibit conversation. Many patients don't feel comfortable talking about painful periods, don't feel comfortable talking about painful bowel movements, don't feel comfortable talking about painful intercourse, and many healthcare providers don't either.

The other thing, as I mentioned earlier, is pain is very subjective. How do you know if your menstrual cramps are a lot worse than someone else's? And almost uniformly when talks to their family member, or sometimes healthcare providers, it's dismissed. Menses are supposed to hurt. Take a Motrin – just toughen up and get back to work. It isn't – sometimes these patients are really quite disabled before they get the attention to make that diagnosis. We need to really take this seriously.

As I mentioned earlier, these symptoms are often non-specific or systemic, and associated sometimes with other diseases. But we can't dismiss them, we can't go on a wild goose chase, looking at some of these other symptoms. We need to know that this constellation of symptoms really points to the diagnosis being endometriosis. I can't tell you how many patients of mine have come to me, having seen a psychiatrist first, a urologist, a gastroenterologist and had a colonoscopy, before they come see me for a diagnosis of endometriosis.

In one survey of over 7,000 women, 65% - nearly two-thirds – were initially misdiagnosed, and nearly half had to see at least five physicians before they could get the correct diagnosis. We can do better, and what we'll talk about today is how to do a better job diagnosing endometriosis, because an early diagnosis, an early treatment, can reduce their uncertainty, can reduce the discomfort and hopefully stop disease progression. This is a disease that often affects women early on in their life. It really limits their school performance, it may limit their early career performance, and those are things that you really can't redo. You don't get a do-over on your education. It's important we recognize this early and start to treat early so we can help them reach their full potential in life.

Again, some of the challenges in making the diagnosis are listed here. The patients are often hesitant to bring up, due to their either past disappointments or they haven't been heard. The stigma associated with some of the types of issues that we've talked about. The diagnosis is often missed. Again, the varied physical manifestations can be confusing. Superficial lesions versus the deep infiltrating disease, the severe dysmenorrhea can be confusing. Non-specific symptoms can be also confusing. We mentioned some of the multitude of symptoms that can be all endometriosis-related.

In the past, we relied on surgical diagnosis, and I think we're moving towards clinical diagnosis. That put a huge barrier in place. If we had to tell someone they had to go through a surgery before they could get a diagnosis of endometriosis, well obviously, only the most severe would get to the point where they wanted surgery to make the diagnosis. We can do a better job detecting this earlier.

We also need to increase awareness, both the public and healthcare professionals. I think OB/GYNs have a pretty good sense of endometriosis, but many others don't, including some pediatricians, who are often the first to see these young women when they start to develop endometriosis symptoms. A lack of awareness is a big problem, and the more we can do to promote awareness of this condition, the better we'll do taking care of these women and recognizing the disease early.

The clinical presentation, again, the average age of diagnosis is about 28 years. About half are diagnosed between 18 and 29, but again, there's a huge delay. 90% almost, are symptomatic for years before we make the diagnosis, and women with endometriosis are two to three times more likely to have symptoms of other painful conditions. Many have these other coexisting conditions, or indeed, many of them may be manifestations of endometriosis that just haven't been recognized. That central sensitization of pain makes them more sensitive to other types of painful stimuli. And again, it isn't just someone being overly sensitive. Endometriosis actually increases pain sensitization. We've proven that in animal models, that the pain sensitivity increases when you get endometriosis, as the endometriosis progresses.

Risk factors for this disease include family history. You're approximately seven-fold higher risk if a first degree relative is affected, early menarche is a risk factor, frequent or heavy menses – all these things increase – retrograde menstruation – and increase the likelihood of endometriosis. Nulliparity is a risk factor, pregnancy is a good treatment for endometriosis. There's an association of endometriosis with autoimmune conditions. There are genetic contributions, again as we said, family history is important. There is no single endometriosis gene that we can test for, but there are certainly a multitude of genes that contribute to getting endometriosis, and certainly that's something that can run in families. And there's a higher incidence in women with fibroids.

There is a significant decrease in quality of life. Again, the chronic pelvic pain we talked about, dysmenorrhea, deep dyspareunia is common, dysuria or painful urination is common, dysphasia, fatigue is very common, infertility we talked about, and we also talked about that pain amplification that is a consequence of endometriosis. These women may be more sensitive to multiple painful stimuli.

There are other conditions which we can sometimes confuse with endometriosis, and I'd like to think that most of us would be able to distinguish these. I think most gynecologists can. Pelvic inflammatory disease, yes, causes pain but it's often associated with fever, elevated white count, relatively rapid onset, doesn't vary with the menstrual cycle. Same with adhesive disease – doesn't vary with the menstrual cycle. Cysts we can diagnose on ultrasound. Fibroids we can feel or diagnose with ultrasound, same with adenomyosis. History of sexual __(15:47), commonly associated with pain but we can get that on a good history.

I'd like to think that we can sort out the difference between a disease that causes cyclic pelvic pain, at least initially, and these other chronic conditions that aren't necessarily cyclic in nature. Matter of fact, I'd like to make it relatively easy to diagnose pain that is associated with endometriosis. The chronic pain with endometriosis is a cyclic and progressive pain. I think we know that endometriosis tends to start as painful menses or dysmenorrhea. That's cyclic – the pain comes and goes with menstruation. Over time, yes, the character of that pain can change. It can get worse. It can happen at times other than with menses – during the menstrual cycle, or it can even become constant through the menstrual cycle. But this is a disease that characteristically starts as cyclic pain, often as

dysmenorrhea.

Second, pain progresses over time. Endometriosis is not a disease that we have from menarche immediately. It comes through accumulating retrograde menstruation, so it's classically progressive. I'd like to suggest to you that anybody that has cyclic and progressive pelvic pain almost certainly has endometriosis. People with cyclic, progressive pelvic pain – I think we can make the clinical diagnosis of endometriosis and start empiric treatment. We will almost always be right, in well over 95% of the time.

If they have cyclic bladder or bowel associated symptoms, well, those are more likely to be endometriosis than a primary bowel or bladder problem. Primary bowel and bladder problems don't tend to be cyclic in nature. They don't vary with the menstrual cycle. They are more likely to be endometriosis affecting these other organs than a primary condition affecting these organs. So again, anybody with cyclic and progressive pelvic pain – you will usually be right if you make a presumptive diagnosis of endometriosis and can begin empiric treatment.

Clinical diagnosis and treatment is important. Endometriosis, as I've mentioned, is biologically very complex. It's a chronic systemic disease. It has multiple presentations. However, clinically I think if we focus on that definition that I just gave you, it is relatively easy to recognize the disease, and easy to become – begin an initial empiric treatment. Anyone with that cyclic and progressive pelvic pain, most likely has endometriosis and a trial of endometriosis therapy is warranted.

Ultrasound or MRI can add to your capabilities of diagnosing this. We can see the endometriomas on ultrasound – relatively easy way to find endometriomas – and we're getting better at detecting some of the deep infiltrating endometriosis on ultrasound or MRI, but still, most endometriosis is superficial, and peritoneal lesions are the most common. You can't see those on any imaging technique, and while imaging may be helpful if ruling out other conditions or finding those big endometriomas, you can never rule out endometriosis with an imaging technique.

So, endometriosis is now clinically diagnosed initially. I reserve surgery for case that don't respond to medical therapy, or if we're unsure of the diagnosis – a large pelvic mass or maybe acute and sudden onset presentation that is consistent with that progressive history of endometriosis. Of course, there are other individualized indications, but most of the cases I do now are for women who failed to respond to medical therapy, after I've tried first and second line medical therapies. I think you design therapies that address the woman's complaint, but also know that this is a chronic and recurrent disease. We have to think about a bridge to suppression, to prevent recurrence. A surgery may be a quick fix, but the disease will commonly recur unless medical therapy is used to prevent those recurrences. I think why not just try the medical therapy if we're going to need to be on it anyways for the long run. Try initially – if it works and you can avoid the surgery, that's a good thing.

So what are the medical approaches? Well, the treatment options for endometriosis have traditionally included first-line progestins with a nonsteroidal anti-inflammatory, together with either an oral contraceptive or a levonorgestrel intrauterine system. Oral contraceptives are, by far, the most common first line, and it the progestin in those oral contraceptives that are effective.

Now we have some new second-line therapies. Traditionally the second-line therapy that was most commonly used was a GnRH agonist, such as leuprolide. Now, we have the GnRH antagonists which have made second-line therapy a much easier thing to administer. These are oral agents that we'll talk about in much more detail in a few minutes. Other investigational second-line therapies include selective progestin receptor modulators which are not approved for use in the U.S., Selective estrogen receptor modulators which are approved for this indication, aromatase inhibitors are still occasionally used off-label. Surgical approaches include laparoscopic excision where we remove the endometriosis, or in extreme cases, definitive therapy for someone who's completed childbearing can include hysterectomy.

Let's talk about the surgical approaches. Again, laparoscopy typically with excision can provide effective and immediate pain relief, but not everyone responds. Either failure to respond entirely, or partial response – not everyone responds to the laparoscopic surgery. And most patients will have a recurrence – in some studies, up to half, within two years. Younger patients who are going to have to deal with retrograde menstruation for the long term are very likely – almost inevitably going to find that a recurrence comes sooner or later. Potentially, somebody who's older, approaching menopause, may not recur, but the vast majority of patients, this does recur. So, medical therapy should always be used after laparoscopy to suppress the endometriosis and delay or prevent recurrence.

Of course, the other surgical approach that we mentioned is hysterectomy. That is never my first choice. It is always a last resort, for women who have not responded to other treatments – either medical therapy or laparoscopy.

It's certainly beneficial for pain relief. It is not completely curative, especially if the ovaries are left in place. We do recommend ovarian preservation, especially for women less than 40 years of age. But of course, those who have recurrence, or in those who are over 40, or those who want to have the highest success rate, oophorectomy can be included, and hormone replacement therapy should always be used in these younger women. Typically use progestins, at least initially, even after hysterectomy to prevent endometriosis recurrence,

tapering that off after six months to a year.

Medical therapy focuses on either reducing estrogen, which stimulates endometriosis, or blocking estrogen action. So the medical therapy can be suppressing, again, estrogen production from the ovary, or things that block estrogen action, which include progestins. Progestins not only block estrogen production, but have a direct effect on the endometriosis cells themselves, causing a differentiation or decidualization, but also blocking the proliferative effects of estrogen, and the inflammatory effects of estrogen, on the endometriosis cells. Again, oral contraceptives are a first-line agent, and it's the progestin in the oral contraceptive that's effective. It gives you that progestin effect. It can be either administered in the traditional fashion cyclically, or I prefer to use them continuously. If you have dysmenorrhea, why have menses at all? We can use a pill continuously to eliminate menses. No placebo, no break.

I think birth control pills are best for the milder pelvic pain of endometriosis. They are also good in that they provide contraception, but we can't forget that they also have some side effects – mood changes, anxiety, depression, bloating or breast tenderness are common side effects. And important to remember that some women will have some pain relief oral contraceptives, but may be having some troubling side effects. These are also women we should think about second line therapy. But the big problems with progestins is that some endometriosis is resistant to progestin. Not only that, the side effects that we mentioned, that could lead one to move to a second line therapy, but some just doesn't respond at all.

This is a study done by Valerie Flores, my colleague who worked with me here at Yale, and she looked at the progestin receptor levels in endometriosis lesions of women with endometriosis, and she compared those that responded to a progestin – usually an oral contraceptive – or didn't respond. And you can see, when they had a very high progestin receptor level, as shown on the left, they all responded to a progestin-based therapy. On the right, you can see those with very low PR – very low progestin receptor. You had a very, very low response rate. So some endometriosis just isn't going to respond to a progestin. They have very low receptor, and switching from one progestin to another, or trying one pill or another pill, just doesn't make sense. They're not going to respond to any progestin. It's because the progesterone receptor is very low. We really need to think about moving on to a second line agent.

Other things that are used commonly – danazol – isn't used frequently anymore due to the androgenic side effects. It's effective, it's FDA-approved, however the thought of acne and hair growth is just not appealing to most patients, so rarely used today.

Aromatase inhibitors have been used off-label, but again, these have to be used with another agent. Aromatase inhibitors block estrogen production, but they lead to increased FSH, ovarian stimulation, cyst formation. You should really only use these in conjunction with other drugs. They're never a standalone therapy.

The second line therapies that typically are much more commonly used today are the GnRH antagonists – elagolix, relugolix and linzagolix in development for this indication are all agents that we'll talk about in a lot more detail now. And because endometriosis is complex, it sometimes is a bit intimidating. Doesn't always respond to progestins, but it's always estrogen dependent. It always goes away with menopause. So, agents that lower estrogen tend to be the most effective drugs for this disease.

These days we're using the GnRH antagonists. Now, the GnRH agonists that you're familiar with – it's the agents such as leuprolide – stimulate the GnRH receptor initially, and the GnRH receptor is meant to see pulsatile release of GnRH. When we give GnRH in a continuous fashion such as with GnRH agonists, after initial stimulation of the receptor, it becomes desensitized and down regulated, and no longer responds. But you have to overstimulate the receptor to get it to turn off. There is no titration. It's all or nothing response – either full response or complete menopause, estrogen levels down near zero. So we don't have any flexibility. It's a very vigorous response, and initially we get this flare effect, where estrogen levels actually go up and the disease can get worse.

The GnRH antagonists are now available orally. They're nonpeptide antagonists that result in dose-dependent suppression of gonadotrophins, and ovarian sex steroids, namely estrogen. Again, you can give a little bit and get a partial response, you can give a lot and get a complete response. They don't desensitize or down-regulate the receptor. And they also work very rapidly. You don't have to go through that flare effect. They work within about 24 hours, to suppress estradiol levels, and they also can be reversed just as quickly, so appropriate for somebody who may be considering childbearing in the near future.

So again, this looks at the first generation antagonist that was commercially available – elagolix. You can see what happens, but within 24 hours, at the low dose you can suppress estradiol just a little bit. There the average is 42 picograms/ml. Put you in a lower dose – rather in a lower estradiol state – that can held control endometriosis. But for those that need further suppression, you can use the 200 milligram twice a day dose. You get an average estradiol that's 12 picograms/ml.

Not the zero that you'd get with GnRH agonists, but you can titrate the dose to give just as much suppression of estradiol as an individual patient needs, and it can vary, and it gives you the ability to titrate dose and get just the amount of relief that you need.

This diagram looks at how that might work, how we can use that to our advantage – the GnRH antagonists, to titrate estradiol levels to

just what we want. The gray area in the top shows the higher estrogen levels that one might get during a normal menstrual cycle. Those are high enough to stimulate endometriosis and cause symptoms. The blue on the bottom looks at complete suppression, and you get very, very low estradiol levels. You might get bone loss. You might get vasomotor symptoms – hot flashes. And that Goldilocks zone is shown here in green, where you can get estradiol levels just low enough that you can control the endometriosis, but not so low that you start to get bone loss and hot flashes. On the far left, the untreated group shows the variable estrogen levels that you get during a normal menstrual cycle, that stimulate endometriosis.

The second shows GnRH agonists. Again, we don't have that ability to titrate. You get full suppression. These injectable agents give you an all-or-nothing response – full suppression – in the area we get vasomotor symptoms and side effects. The GnRH antagonists, on the other hand, you can titrate. So you can give a low dose and bring that level just down enough to perhaps control the endometriosis without side effects. You can give a high dose and suppress someone to a lower level that is quite effective at suppressing endometriosis, and then you have the ability to use add-back therapy, to restore estradiol levels, not to the high levels that would stimulate endometriosis growth, but just to that perfect range where you don't stimulate growth of endometriosis, but prevent hot flushes, prevent side effects such as bone loss.

So let's talk about the GnRH antagonists that are commercially available, FDA-approved. The first was elagolix, again an oral GnRH antagonist. It's been out for about four years now in the United States, and proven to be highly effective. These are the two double blind, placebo controlled, randomized clinical trials that we conducted, that led to FDA approval of elagolix for the treatment of endometriosis. The two trials were nearly identical. One was conducted in North America and one was a global trial. In order to enroll in these trials, women had to have been in the premenopausal age range, had to have surgically diagnosed endometriosis, and had to have – importantly – moderate to severe dysmenorrhea and also concomitant non-menstrual pelvic pain. So these were not the patients with very mild pain. These were the moderate-to-severe, with non-menstrual pelvic pain as well. Most of these women had tried other therapies prior to enrolling in the trial.

So after a washout period, if they were on other therapies, they underwent a screening period of two cycles, where their baseline pain was recorded, and then they were randomized to either receive six months of placebo, six months of elagolix at 150 mg once a day, or six months of elagolix at 200 mg twice a day. And then there was an extension study that followed them out for a full year.

These are the results of these trials. Again, the two different trials are shown on the right and left, and you can see the results are essentially identical. The top shows the placebo in green. There is a bit of a placebo effect. The low dose of elagolix is shown in the brown in the middle. And the high dose of elagolix is shown in the blue at the bottom. Now this looks at the change in baseline dysmenorrhea scores. It's important to notice, noted here, the baseline dysmenorrhea score is 2.2. This is a scale that was either 0, 1, 2 or 3. No pain, mild, moderate, or severe pain. Again, as I told you a moment ago, patients had to have had moderate to severe pain to enroll in this trial. So the score was 2.2 and it's between moderate-2, severe-3. Notice on the high dose of elagolix, the score went from an average baseline of 2.2 down by about 2 points. So you can see, from 2.2 down almost 2 points, these women were really very comfortable when we used the high dose of elagolix. We got a decrease of about 1 point with the lower dose of elagolix – again, a nice response for those who don't want to take the high dose. But I also would remind you again, these are patients with moderate to severe pain. I tend to use the higher dose for those with severe pain, and use the lower dose for those with the lower levels of baseline pain. We find it to be quite effective.

This looks at the proportion of responders rather than looking at just the average change – the proportion of responders at the two different doses, ad this looks at both the six-month and one-year time period. Let's look at the two different studies. Again, the results are nearly identical. At 12 months, we see at the low dose, 50% response for dysmenorrhea improvement, and this had to be a clinical and statistically significant response. And these patients had to really feel that this was significantly improving their comfort levels, and have it be statistically robust. So these patients felt well – half at the low dose, and again about 75% or more at the high dose. So again, most patients responded to high dose. And again, I use lower dose for those with a milder pain, where you'll see a higher response rate, but even here, half of them responded to low dose, with very minimal – as we'll show you in a minute – side effects.

When we look at non-menstrual pelvic pain, get a little harder to treat than dysmenorrhea, but you see two-thirds, approximately, of them responding. And if we look at dyspareunia – probably the most hard symptom to treat, most difficult to treat – we see nearly half responding at the low dose, and closer to 60% at the high dose at the end of a year. So again, very high response rate – higher at the high dose, but again, these are patients with moderate to severe pain. We'll see an even better response in those with milder forms of pain.

Side effects, of course, are something we need to pay attention to. There were no difference in adverse events, aside from the ones that were listed here, between placebo and elagolix. Again, those that occurred in at least 15% in one treatment group included hot flashes – not surprisingly. As we lower estrogen levels, we see more hot flushes in the low dose elagolix group, and even more in the high dose

elagolix group. But important to note that the majority of these hot flushes were mild in both treatment doses, and the discontinuation rate for hot flushes was under one percent in the low dose group, and under three percent in the high dose group – very different than what we saw with the old-fashioned GnRH agonists – the leuprolide treatment – we had huge numbers of women dropping out of the studies because of the profound side effects. The side effects are quite tolerable.

But even more importantly, what I do is I treat vasomotor symptoms like I do with anybody who has vasomotor symptoms. When someone goes into menopause, I give them hormone therapy. Here, I use add-back therapy if somebody has vasomotor symptoms, like I would treat any other woman having vasomotor symptoms. These trials were not done with add-back therapy, but in real life, we can use them.

Relugolix – just recently been approved – as well, another GnRH antagonist. They use a little different approach here. Relugolix comes in one dose, and it is a fully suppressive dose, with add-back therapy built in. So everyone gets add-back therapy. The dose is 40 mg, and it includes estradiol and norethindrone. And you can look in the two trials that led to approval of this drug for endometriosis, we see a response rate for dysmenorrhea. Again, similar to what we saw before, about 75% response rate, and about a 60% response rate to non-menstrual pelvic pain. So again, similar efficacy. We see minimal decrease in bone mineral density – again because the add-back is included. So, we have a drug that has relatively few side effects. It's a simple, once a day drug, little different approach – add-back built in, but a very convenient approach for some patients. It doesn't give you the flexibility of dosing, or deciding when to use add-back, but a simple regimen that may be appealing to some patients and providers. So, I think the important point that we should think about, when talking to our patients, that this really is a complex disease. We have to take it seriously and there are multiple treatment available.

The principles of shared decision-making are crucial here. The shared decision-making approach is one in which the clinician and patients communicate, to give the best available evidence and help guide our patients to making the right decisions. The steps include introducing choice. Surgery versus medical therapy. Different medical therapies. Describing the options. And include listening to the patient, their preferences, and supporting them in their decision. Helping the patients explore these different preferences in making these collaborative decisions.

We need to understand the risks associated with the condition, the risks associated with the treatment options – including the benefits, risks, alternatives and uncertainties – and weighing their own personal values and personal preferences – what matters most to the patient, what matters to them as an individual. Patients will have very different and strong opinions about what type of treatments they want to use, and it's our job to properly inform them and guide them. We need to participate in this decision-making, again, as a shared process.

So in general, what do we do? We need to recognize endometriosis early on. We do that by listening to our patients. Listen to their goals for treatment. Listen to their past experiences, which almost always include having had their pain dismissed, and making sure we alleviate their fears. They're going to be fearful that they won't be taken seriously, and they're also used to having their diagnosis confused with all of these systemic effects of endometriosis. We really need to think clearly that all of these symptoms that they're feeling are related to their endometriosis. We can't dismiss them. We need to validate them. Your patients will really trust you and feel very grateful that you have understood them and put together all of their symptoms in this one diagnosis. That will help you develop a relationship, a trusting relationship with your patients, and allow the type of teamwork that's necessary to treat this disease. Again, decision aids are often very helpful. It becomes confusing, but to start to lay out this framework of what options are available to them – all of their choices, when appropriate – very helpful. Think about using tools to help assess their pain and all of their symptoms. There are many tools available that you can use to put together all of their symptoms and help decide which ones are truly related to endometriosis, and again, not dismiss all of these other symptoms as unrelated. They may all be due to the endometriosis, and really just reinforce the endometriosis diagnosis.

Talk about different treatment options – the risks and benefits. Explain the goals of therapy, not only to alleviate their pain, but alleviate many of these other symptoms. But importantly, to prevent recurrence. We don't have a cure for endometriosis. We need to think about this as a chronic disease that we manage until the time of menopause. Make sure that they're clear that that is the goal, not only to alleviate pain – I would say eliminate pain, my goal is always zero pain – but also prevent recurrence, maximize their ability fully enjoy life, and to lead a fully productive life.

We need to start thinking about personalizing treatment. Often someone with very strong opinions about what types of treatments they want to use – they may have had an experience with side effects from progestins and birth control pill before – important to take that seriously when considering what options to use for medical therapy. And describe the common risks, including all of the risks and misperceptions that someone may have.

I think one of the most common myths about GnRH antagonists, for example, they are not as severe. They do not have the side effects. They're milder, gentler treatments compared to the old-fashioned agonists that we've used in the past. And I think we need to closely

monitor these patients. This is not the kind of disease where you give them a medication, say see you next year for your annual exam. Now we need to really monitor them, to see how they're doing, look for compliance, look and see how effective they are – these treatments are, and be ready to move to second-line therapy.

So let me conclude with saying that endometriosis really has quite a varied presentation. The diffuse symptoms have really made it difficult to diagnose this for some practitioners. I think we need to make the effort to diagnose endometriosis early, and we can do that by recognizing all of the different manifestations of the disease. Again, not dismiss those as other diseases, but really get them to the right diagnosis and to diagnose them empirically, diagnose them clinically, and start empiric treatment. And while surgical therapy may treat the local disease in the pelvis, as I started earlier on to explain, this is not a disease confined to the pelvis. This is a systemic disease, and medical therapy may be needed to treat systemic manifestations of the disease. Not only that, it's needed to prevent recurrence, even in those who elect surgical therapy.

And importantly, while oral contraceptives are often an effective initial therapy, they are still the first-line therapy for endometriosis. The GnRH antagonists have really changed our approach to endometriosis. We now can offer a new, patient-friendly option for those who either fail oral contraceptive therapy or have side effects from oral contraceptives. Or I even use it as first-line therapy for those with very severe pain.

So, I thank you. I think we need to advocate for these patients, and I think we can make that clinical diagnosis and get them treated early. They don't need to wait years for a definitive diagnosis. We can really give them back those lost years of their lives, where they may be held back in school and early career, and never reach their full potential. Let's give them their lives back. Thank you.

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