Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/pain-points-weighing-the-benefits-and-drawbacks-of-the-gnrh-antagonists-throughout-the-endometriosis-treatment-journey/24399/

Released: 08/09/2024
Valid until: 08/09/2025
Time needed to complete: 30 minutes

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

Pain Points: Weighing the Benefits and Drawbacks of the GnRH Antagonists Throughout the Endometriosis Treatment Journey

Announcer:
Welcome to CME on ReachMD. This activity, titled “Pain Points: Weighing the Benefits and Drawbacks of the GnRH Antagonists Throughout the Endometriosis Treatment Journey” is provided by Omnia Education.

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

Dr. Shulman:
GnRH antagonists have begun to make a real difference in the pharmacologic management of endometriosis. And for many women, they may represent a good first-line option when compared with surgery. Today, we'll be having a discussion with Dr. Ayman Al-Hendy from the University of Chicago and Dr. Suzie As-Sanie from University of Michigan, in which they'll be addressing the benefits and disadvantages associated with first-line use of GnRH antagonists in the management of endometriosis.

This is CME on ReachMD, and I'm Dr. Lee Shulman. I'd like to welcome Dr. Al-Hendy to our discussion today. Welcome.

Dr. Al-Hendy:
Thank you, Lee. It's great to be with you today.

Dr. Shulman:
Great to have you here. I'd also now like to introduce, from home, Dr. Suzie As-Sanie. Suzie, welcome to the program.

Dr. As-Sanie:
Thank you, Lee. It's nice to be joining you and Ayman Today.

Dr. Shulman:
Great. Let's begin our discussion.

Suzie, endometriosis is a chronic inflammatory disease for many women of reproductive age and one that should be considered a public health issue. The gold standard for diagnosing endometriosis has long been laparoscopy and/or some sort of invasive surgical intervention with histologic review, but that really has been changing dramatically over the last few years. Can you discuss this with our learners today?

Dr. As-Sanie:
Thank you, Lee. That's a really important point and really the highlight of some of the important ways that we've sort of changed our thinking about the diagnosis of endometriosis. So Agarwal and colleagues in 2019 published an article on the call to action related to the clinical diagnosis of endometriosis. And this was a really insightful article that reflected on the current view that the gold standard for diagnosing endometriosis is by laparoscopy with or without histologic evaluation. But what this publication and many other experts stress is that endometriosis diagnosis really should not focus specifically on the lesion but should really focus on the symptoms and the characteristics of the disease, which is that it is a menstrual cycle-dependent chronic inflammatory as well as systemic disease that

commonly presents as pelvic pain. We really should be emphasizing the symptoms as well as the origins of the condition. And so this definition really creates a path to clinical diagnosis for endometriosis in which we can initiate medical therapy without having to put patients through an invasive surgery just to make the diagnosis. And the hope is that this will likely result in the shortening of the time from symptoms to diagnosis compared to having to wait for a surgical confirmation.

Dr. Shulman:
Suzie, did Agarwal and colleagues provide an algorithmic path to follow when making a clinical diagnosis for endometriosis?

Dr. As-Sanie:
Yeah, so as a matter of fact, Agarwal and colleagues provided a 4-part clinical diagnosis algorithm, which is really the standard of care that we should be considering in the evaluation and treatment of patients with symptoms. And so the first step is to evaluate the symptom presentation with a strong focus on the symptoms of painful periods, non-menstrual pelvic pain, dyspareunia, and infertility. We should review the patient's history that points to those symptoms. What exacerbates those symptoms? Do they have any other associated symptoms? What is their family history? We know that endometriosis does have a predisposition in patients with a family history of that diagnosis. Next, we need to perform a detailed physical exam looking for signs of the condition as well as finally ordering imaging, either ultrasound and sometimes MRI, to confirm the diagnosis.

So the argument for using imaging as part of the clinical diagnosis of endometriosis is definitely supported by a number of high-impact publications in the last several years. So these include Pascoal and colleagues in 2022, Bausic and colleagues in 2022, Testini and their group in 2022, as well as Becker and colleagues with the ESHRE [European Society of Human Reproduction and Embryology] guidelines, published around that time.

Agarwal and colleagues concluded that there really should not be a single gold standard diagnostic method for endometriosis but, rather, multiple accepted diagnostic methods that are appropriate for different circumstances. And so we know that imaging is incredibly helpful. It has really excellent sensitivity and specificity for the diagnosis of ovarian endometriosis disease as well as deeply infiltrative disease. And when we see imaging characteristics of that, we can be really certain that the disease exists. It's just really important to point out, though, that the lack of imaging findings of endometriosis does not exclude the diagnosis because we know that most of these imaging techniques, at least to date, are not sensitive and specific enough for the most common form of endometriosis, which is superficial disease.

And so if we see normal imaging but patients still have the symptoms of endometriosis, it would be appropriate to still give that patient a clinical diagnosis of endometriosis and initiate therapy when appropriate.

Dr. Shulman:
Suzie, I can't thank you enough. Endometriosis has long been a challenging diagnostic process for many clinicians, and the information you provided us here today really gives us a far clearer path to an accurate assessment for patients suffering from the symptoms associated with endometriosis.

Ayman, now that we've discussed the value of a clinical diagnosis for endometriosis, let's turn to another changing paradigm. I'm focusing on the view that medical intervention, as opposed to surgery, is not only an appropriate first-line option, but also an important part of the critical continuum of care many women require during their endometriosis life journey.

Dr. Al-Hendy:
Absolutely. I agree with you, Lee. Now when we shift to the treatment – we talked about the diagnosis; now we'll talk about the treatment – endometriosis, probably like other benign gynecologic conditions such as uterine fibroids, have been considered surgical conditions traditionally because there was no viable, high- quality products or medical therapy that's based on high-quality research. Now that has changed, and I would say the change started by the ASRM [American Society for Reproductive Medicine] practice guidelines from 2014 and even more now that we have 2 FDA-approved oral treatments for endometriosis. What I'm talking about is the oral GnRH antagonists. Now with this availability of medical treatment options based on high-quality phase 3 clinical trials, I think the paradigm should be shifting.

In many of my talks, I talk about, now, endometriosis becoming a chronic medical condition. This medical treatment therapy provides a viable option for these patients once you confirm the diagnosis, also based on clinical judgment, with no need for diagnostic laparoscopy. It just makes sense, then, to move into noninvasive medical treatment options that can put the disease in remission and relieve patients' symptoms without exposing them to surgery.

And I would say that, like any other disease, like the way we teach our medical students and residents and fellows, we should always start with simple, noninvasive treatment options for the patient and only move to more invasive surgical treatment options when either

the patient is not a good candidate for the medical therapy or the medical therapy failed.

Dr. Shulman:
Ayman, you mentioned that ASRM 2014 practice committee statements that addressed the issues related to repeated surgeries and surgery in general for endometriosis and correlated repeated surgeries with the desire for pregnancy. Is that correct?

Dr. Al-Hendy:
That is correct. And to be specific, let's actually go through what the practice committee particularly covered. They mentioned that multiple surgical procedures should be avoided whenever possible because surgery has inherent risk and might result in adhesion that can cause pelvic pain, decrease ovarian reserve, and actually, by themselves, the adhesion, the postoperative adhesion, can cause infertility by themselves. And women of reproductive age with endometriosis should be encouraged to pursue pregnancy, of course at their own pace, at their own time, but at the earliest time that life circumstances allow.

Dr. Shulman:
Ayman, thank you so much. It's been a really interesting discussion on an incredibly important assessment of the change in our approach to the treatment of endometriosis.

Suzie, do you have anything to add to that?

Dr. As-Sanie:
Thank you, Lee, for the opportunity, and I fully agree with all of the points that Ayman made. Maybe just a couple points that I would also add is that as someone who focuses on the evaluation and treatment of pelvic pain in general, I think one of the most critical things to consider when treating a patient with pelvic pain in which we have a high suspicion for endometriosis is that whether or not somebody actually ends up having endometriosis, our treatment algorithm is often similar with starting with medical therapy. And because we know that medical therapy on average is relatively equivalent in efficacy to surgical therapy for many patients with endometriosis, beginning with medical therapy should really reassure the patient that regardless of whether or not they have endometriosis, any type of pain that worsens with the menstrual cycle is often effectively treated with some method of hormone suppression. So beginning with medical therapy is really an important first step for most patients with these symptoms.

There are some certain circumstances in which medical therapy is not appropriate. And with our diagnostic algorithm of looking at symptoms as well as doing imaging, we should be able to catch these patients from the beginning. And those include patients with enlarging ovarian masses, patients with deeply infiltrated endometriosis in which there's concern for urinary tract or bowel-obstructive symptoms. Those patients are really a small subset of patients who need to go to surgery prior to medical therapy. But for the vast majority of patients, medical therapy is really a very appropriate place to begin treatment.

Dr. Shulman:
Suzie, thanks so much for your response.

For those just tuning in, you're listening to ReachMD. I'm Dr. Lee Shulman, and today we are joining a discussion with Dr. Ayman Al-Hendy and Dr. Suzie As-Sanie. They're just about to delve further into the use of GnRH antagonists in the management of endometriosis.

Now let's move on to our next topic. Suzie, before we delve a bit further into the use of GnRH antagonists in the medical management of endometriosis, can you discuss the estrogen threshold theory and how the GnRH antagonist mechanism of action fits into that theory?

Dr. As-Sanie:
Thank you, Lee. And this is really an important point. So the estrogen threshold hypothesis was first presented by Dr. Barbieri in 1992 and then gave more detail in 1998. And the idea of the estrogen threshold hypothesis is that endometriosis and some other gynecologic conditions are estrogen-dependent diseases in which estrogen is the key hormone that is important in both the development, progression, as well as persistence of disease. And when estrogen levels are reduced, those diseases, including endometriosis, often regress. And so endometriosis is known to be a very estrogen-responsive disease. And the pelvic pain as well as associated inflammation, in which that's key for the cause of pelvic pain, improves when estrogen production is reduced. Unfortunately, if you reduce estrogen levels to menopause levels, that's associated with many adverse side effects, such as vasomotor symptoms, with hot flashes and vaginal dryness, and eventually significant and irreversible bone mineral density loss.

Dr. Shulman:
Suzie, that was great information for our listeners. It's interesting, though, but the estrogen threshold hypothesis was first discussed in 1992 and then further elaborated on in 1998. But what is the actual clinical support for the theory?

Dr. As-Sanie:

Yeah, so that's a great question, and there's actually quite a bit of clinical support for the estrogen threshold hypothesis. So first, in women with endometriosis and pelvic pain, the combination of removing both ovaries, so bilateral oophorectomy, plus giving them a low dose of estrogen treatment after surgery has been shown to produce sustained improvement in pelvic pain symptoms as well as reductions in the hypoestrogenic effects of removing both ovaries or bilateral oophorectomy. In a parallel manner, we also know that chronic GnRH agonists with treatment plus low-dose steroid therapy, which would include estrogen plus progesterone or norethindrone acetate, is very effective in the treatment of pelvic pain caused by endometriosis and reduce the hypoestrogenic effects associated with those low levels of estrogen caused by the GnRH agonist. So from these observations, Barbieri proposed that an estrogen threshold hypothesis suggests that there might be this really critical window in which circulating estrogen levels should be low enough to prevent disease stimulation, such as endometriosis, but high enough to eliminate the related side effects, such as those vasomotor symptoms, vaginal dryness, and bone mineral density loss. So we're really looking for that sweet spot in order to manage a patient's symptoms effectively with minimizing these adverse side effects.

Dr. Shulman:
Suzie, again, great information for our listeners. Can you put the estrogen threshold hypothesis into some perspective as it relates to our discussion today about GnRH antagonists?

Dr. As-Sanie:
Certainly. So first, GnRH agonists, which are medically effective but have some limitations in their mechanism of action. So with the agonists, there's additional stimulation that leads to symptomatic flare with the initial rise in estrogen levels. Second, desensitization state leads to full suppression of estradiol with very little option to titrate estrogen levels, and so you basically have complete suppression of estrogen without any ability to titrate. And then finally, there is unpredictable reversibility upon use of the depot formulations. And so for many patients with those depot formulations, there can be a pretty long delay to the resumption of normal menses, which can definitely be a negative aspect to patients who are trying to become pregnant immediately after stopping these medications. So when you think about GRH antagonists, these also work very effectively, but given their different mechanism of action, this has some significant clinical benefits to patients.

So first, you can produce a dose-dependent estrogen suppression with the antagonists. You see a much more rapid reversibility as well as recovery of hormone secretion with a quick recovery to regular menses after discontinuation of these medications. And we also don't see a flare response with that flare of estrogen levels and potential exacerbation of symptoms before we get to suppression. So because of these differences in the mechanism of action, they really have a different profile that can really have a lot of added value to patients in the right time and place.

Dr. Shulman:
Suzie, thank you so much.

Ayman, now let's turn our attention to data supporting the value of using GnRH antagonists in the early management of endometriosis.

Dr. Al-Hendy:
That's a very important point, Lee, because I believe in the last 3-4 years, our field has seen the largest clinical research programs in the field of endometriosis that we have seen for a long time. So we're mainly talking about 2 specific oral GnRH antagonists. So let's go through that some of the clinical trial data that led to the FDA approval of those 2 medications for treatment of pain related to endometriosis. Let's start with relugolix, for example. So relugolix is an oral medication, and it's FDA-approved as a combinational therapy. So every time I'm going to say relugolix combination therapy, it means one tablet that has 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate, all together in one tablet approved by the FDA for treatment of pelvic pain related to endometriosis once a day. One tablet, once a day. And we'll talk later on about elagolix.

So relugolix combination therapy went through a large clinical research program that's called the SPIRIT program, SPIRIT 1, 2, and then the SPIRIT extension studies. And this is all published, and I would encourage our audience to have a look at the papers for more details, but I'll summarize the data here. So SPIRIT 1 and 2 were your classic, highest quality, highest level of research, phase 3 clinical trials, randomized, placebo-controlled, double-blind. So the patient nor the healthcare provider knew what the patient is on. Was it the active treatment or the placebo? We recruited a large number of patients, about 800 randomized patients, the largest probably in the endometriosis field for many, many years. And they were randomized 1:1 into either relugolix combination therapy versus placebo for 6 months.

So who are those patients? We recruited patients with moderate to severe pelvic pain associated with endometriosis. And the moderate to severe pain level was decided by validated questionnaires called the NRS, or Numerical Rating Scale, the most, popular validated method to evaluate chronic pelvic pain associated with endometriosis.

And we evaluated them for 6 months, and particularly, we looked at the improvement into pelvic pain, both dysmenorrhea, cyclic menstrual pain, and also non-menstrual pelvic pain. And to be considered as a responder to relugolix combination therapy, you have to have at least 2.8 degrees decrease in your pelvic pain symptoms, both the dysmenorrhea and also the noncyclic pelvic pain. Highly stringent primary endpoint.

And even with that, at the end of 6 months, about 75% of patients on the relugolix combination therapy enjoyed significant decrease in their pelvic pain compared to placebo. And this difference was highly statistically significant. Also very important in association with that is that there was no increase in the use of analgesia, both opioid analgesia and non-opioid analgesia. And again, there was no increase in that in the treatment group, the relugolix combination therapy, compared to placebo.

We also looked at other pain-related issues, such as dyspareunia, etc., and that also significantly decreased in the group on relugolix combination therapy compared to placebo. So highly encouraging results. But that's the efficacy.

Of course, with any new treatment, we need to look also at safety. So we looked at very long list of possible adverse events, and also we looked at the bone mineral density. Because of the mechanism of action of oral GnRH antagonists, we wanted to look specifically at that. So in terms of adverse events, there was really no significant difference between the treatment group and the placebo. Both groups had minimal adverse events, such as hot flashes, night sweats. They were really similar between the 2 groups, and they were very infrequent. In terms of the bone, after 6 months, we noticed less than 1% decrease in bone mineral density in DEXA scan on both the lumbar region and the femoral neck region, which was considered clinically insignificant and clinically irrelevant. So the safety profile was also fantastic. So that was for 6 months.

But we also, because we wanted to develop this medication as long-term treatment options for patients with pelvic pain and endometriosis as a viable alternative to surgery, not just like as a temporary fix, so we wanted to look longer than 6 months. So we did an extension study for another 1.5 years. So altogether, 2 full years of evaluation, which is really the longest I'm aware of in the field. So all the patients who successfully completed SPIRIT 1 and 2 went into the SPIRIT extension study for another 1.5 years. And just to kind of summarize the data at the end of the 2 years – again, this is all published, so I would encourage everybody to look at the detailed data. But the efficacy continued to be sustained and reliable and durable for full 2 years. At the end of the 2 years, around 60% to 65% of the patients were still enjoying a significant decrease in their pelvic pain symptoms with no increase in both the opioid or non-opioid painkillers. And that was highly significant, more than the placebo.

How about the safety after 2 years of use? Again, bone mineral density, less than 1% decrease in bone mineral density, which, again, was considered to be clinically irrelevant. So altogether, that summarized the relugolix combination therapy-related data.

So let's now talk about the other oral GnRH antagonist, elagolix. Elagolix, went through, probably, a different evaluation process. Remember what I said about combination therapy? In every tablet, there's relugolix 40 mg, which is the active ingredient, the active oral GnRH antagonist, and also there's 1 mg of estradiol and 0.5 mg of norethindrone acetate. Elagolix was evaluated against endometriosis as a monotherapy, just the elagolix by itself. And it went to evaluation at 2 doses, at 150 mg to be used once a day, and 200 mg to be used twice a day. So a low dose versus high dose. The rest of the description of the program to evaluate elagolix for endometriosis was really similar to what I described before. It was called the ELARIS clinical research program, and it was otherwise similar. We recruited a similar kind of patient and had similar criteria.

So how about the outcome? After 6 months, also these women who used elagolix, whether the low dose or the high dose, enjoyed also significant reduction in their pelvic pain symptoms, both in the dysmenorrhea and also the non-menstrual pelvic pain. So the efficacy was very good.

Now on the safety side, unfortunately, especially on the high dose, there were some important side effects that we need to talk about. Because of the mechanism of action, as you can imagine – because this is monotherapy, there is no additional estrogen – many of the patients, especially on the high dose, the 200 mg twice a day, had some hypoestrogenic side effects, such as hot flashes, night sweats, which was significantly more than the placebo. Also in the bone mineral density, there was significant decrease in bone mineral density up to 5% in some patients, which was significantly more than the placebo arm. That's why elagolix as a monotherapy for endometriosis was approved for short term, especially the high dose, the 200 mg twice a day, was approved only for 6 months.

Dr. Shulman:
Ayman, thank you so much. That was a wonderfully comprehensive overview of the 2 regimens that are currently available in the United States. Great job.

Unfortunately, that is all the time we have for this program today. So again, I want to thank all of you for joining us today. I want to thank Dr. Suzie As-Sanie in Michigan and Dr. Ayman Al-Hendy from Chicago for sharing their expertise and insight. It was great speaking with

both of you today.

Dr. Al-Hendy:
Thank you so much, Lee, and I would say goodbye to our audience at this point.

Dr. As-Sanie:
Thank you, Lee. It was great to be on this program with you and Ayman today.

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

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