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Medical Management of Uterine Fibroids: GnRH Antagonists

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Welcome to CME on ReachMD. This activity, entitled “Medical Management of Uterine Fibroids: GnRH Antagonists” is provided by Omnia Education.
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Dr. Shulman:
In recent years, the management of uterine fibroids has shifted radically, and medical treatment options have truly open new pathways to improve patient outcomes and quality of life. The GnRH antagonists are transforming clinical practices and how we approach patients who often suffer significantly from diagnostic delays and suboptimal management.

This is CME on ReachMD, and I'm Dr. Lee Shulman. I'm joined today by a renowned researcher and clinician and a good friend of mine, Dr. Ayman Al-Hendy, Professor of Obstetrics and Gynecology at The University of Chicago.

Ayman, welcome to the show.

Dr. Al-Hendy:
Thank you so much, Dr. Shulman.

Dr. Shulman:
So let’s dive right in. Can you provide us with a brief clinical case to frame our discussion today?

Dr. Al-Hendy:
I focus on benign gynecology; I see mostly cases with uterine fibroids, endometriosis, adenomyosis, etc. And I think, particularly for the program today, I am thinking of a case that I've seen recently, a 26-year-old G0 who actually came to see me, referred from Indiana. This very pleasant patient already had 2 myomectomies, 2 laparoscopic myomectomies for her uterine fibroids because of her severe symptoms: heavy menstrual bleeding, pelvic discomfort. She was not, and she's still not actually trying to achieve a pregnancy soon, but it was done for symptom relief. And then she was referred to me – so they felt that she should come to our center for her third myomectomy.

To make her surgical history even more complicated, this patient also unfortunately suffered from Crohn's disease, and she had already one open colon surgery.

So we discussed the different treatment options. And she and her mom were so happy and so surprised that there's actually now FDA-approved medical option, nonsurgical option, to the point, actually, that they started to cry when I told them about these other options. They left with a prescription and that was almost like, you know, a revelation for her. She was so happy with that.

Dr. Shulman:
Ayman, I think that this presentation of this young woman is a great example of where so many women who are coming in with symptomatic fibroids, with or without a desire for conception, have been sort of sequestered into surgical options only.

It really behooves all of us to recognize that it's time for all of us to reconsider the management paradigm for women with fibroids and to consider patient values and to optimize quality of life. And obviously, as you described in this 26-year-old woman, this information can truly be life changing.

Now that we understand the potential impact, how do you discuss the treatment options with your patients?

Dr. Al-Hendy:
The way I approached my patient, like anything in medicine, we start with simple options. And then if those fail, or if those are not good options for you, then we move on to the more involved, more invasive options, which typically would include surgery. So that's not any different.

And actually, a few years ago, we coined that term, “medical myomectomy.” We published that in 2017 in the context of these newer treatment options for fibroids.

Most of our patients with fibroids, their main priority is 1 of 2 things or actually both. One is control the symptoms, the heavy menstrual bleeding, the pelvic discomfort, the anemia, the pelvic pain, etc., and/or the fertility issue. If they have been trying to achieve a pregnancy and were not successful, and everything else is fine, so that's considered by ACRM [Atlanta Center for Reproductive Medicine] definition unexplained infertility associated with uterine fibroids. And then the assumption there is the fibroid is contributing to this infertility.

So in both cases, I tell them, why not consider these new FDA-approved options that have been proven to be effective and safe and do what I call medical myomectomy. And then only if that fails, then we can consider the surgical myomectomy. Especially in the infertility patient, I tell them, okay, you've been referred to me to the surgical myomectomy. There's always a little bit of waiting time until we do the preoperative workup and schedule you for surgery. Why not consider medical myomectomy with these newer FDA-approved treatment options, and then after that time we can stop, and there's a very quick return of ovulation, quick return of fertility, and then you can move on and try to achieve that desired pregnancy.

Dr. Shulman:
I think it's important that we start including the patient in this discussion, as we should. What are the patient preferences? Ayman, can you delve a little deeper into how your clinical conversations with patients have evolved and how this ties to these newer treatments?

Dr. Al-Hendy:
If we think of our patient with uterine fibroid, it depends on the age and their needs.

In their 20s or early 30s they are clearly very keen on preserving their future fertility, but maybe they are not trying to achieve a pregnancy right away, but they have the significant fibroid-related symptoms. So I talk to this patient, let's use these new FDA-approved medications as a bridge to pregnancy. So of course, the pregnancy timing would be totally dependent on the patient and her decision and timeline. But let's use these medications to control your symptoms while not affecting the integrity of your uterus, not exposing you to a surgical procedure. And then when you're ready, you can stop the medication. Ovulation returns very quickly, just in 4 weeks.

Then there's the other group that at the other extreme of their productive years, the perimenopausal years. I think these FDA-approved medical treatment options are excellent options to bridge that group of patients into menopause. I tell my patient, your fibroid will just melt away – gradually, of course. I think these medical treatment options are an excellent way to bridge them into menopause where there's no further need for additional fibroid treatment.

And then the last group are really the one in the middle. So let's say late 30s, early 40s, and they are very busy with their family life, with their professional life. I know in that particular group, we’re very quick to say fibroid equals surgery, or fibroid equals hysterectomy. I still like to offer these medical treatment options to that group because you get relief of your symptoms with very little intervention, very little time off your work, your busy life.

Dr. Shulman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Ayman al-Hendy. We're just about to break down the latest research on GnRH antagonists and the implications for our patients.

What can you tell us about the latest clinical trials? And what do our patients have to look forward to?

Dr. Al-Hendy:
This probably will come as a pleasant surprise to us because we are used to the injectable GnRH agonist or analogues. So these are oral because they are non-peptide. So when we take them by mouth, they are not going to be digested or destroyed in the GI tract. So that's a major advantage.

And then the other major difference is these are pure antagonists, right? Not agonist, not analogue, they are pure antagonists. What that means, they go to the receptor, to the GnRH receptor on the anterior pituitary and binds to it immediately and start working immediately. But unlike what we had before as the agonist is that they make things worse before they make things better, or you get this flaring of effect with the symptoms worsening – whether the bleeding or the pain – worsening before they get better. We don't have any of that with those oral GnRH antagonists.

So there are actually 3 members of that family that has been developed. One is elagolix, the second is relugolix, and the third is linzagolix. I'm going to focus mainly on the elagolix and relugolix, because those are the ones that have been FDA-approved in the United States for treatment of heavy menstrual bleeding associated with uterine fibroids. Also, relugolix have been also approved recently by the FDA to treat pelvic pain associated with endometriosis. The same dose, the same formulation.

So first elagolix, or Oriahnn, which is elagolix with add-back therapy, 1 mg of estradiol, 0.5 mg of norethindrone acetate all together in the same tablet. That was the first to be approved in summer 2020. So more than 2 years ago now, that was available to us to use to treat heavy menstrual bleeding associated with fibroids.

And the studies that has led to the approval of Oriahnn is called the ELARIS program. We did the studies in women with symptomatic uterine fibroids; the efficacy was fantastic. Within 6 months, about 75% of the patients responded favorably. And then after another 6 months in the extension study, 90% of the patients had measured decrease in their heavy menstrual bleeding. So really, 9 out of 10 of all the participants showed very good effect. Also, the safety profile was fantastic.

Then with the relugolix combination therapy, or Myfembree, this is, again, the relugolix with the same add-back protocol, 1 mg of estradiol, 0.5 mg of norethindrone acetate. Has been approved in summer 2021, so more than a year ago. Myfembree is only 1 tablet once a day. You just take it 1 time per day. And again, the efficacy was fantastic, almost exactly the same; 75% of the patients showed favorable results after 6 months, and about 90% after 1 year. And also additionally, in the case of Myfembree, we evaluated the pelvic pain or pelvic discomfort using objective validated scale. And at least half of the patients who had significant moderate or severe pain at baseline, actually were pain free after 6 months. So wonderful efficacy studies and results. And also the safety profile was very favorable, not really that different from placebo.

Linzagolix, the studies are done, but it's not yet approved in the United States, so probably not going to talk too much about it.

Dr. Shulman:
I think what you just presented is so critical for our listeners and for clinicians who care for women, because what they need to hear is that there is now an FDA-approved medical approach that does not involve surgery. I think the take-home message, even though we're not there yet, is that this needs to be a part of the counseling of women who are coming in for a variety of issues, symptoms, infertility, not as a second or third choice, but potentially as a first-line, mainstream option for managing symptoms and even for managing infertility.

How do you follow up with your patients about safety concerns?

Dr. Al-Hendy:
The counseling/prescription session is really very simple. And it won't come as a surprise at all to ob-gyns, because we're used to prescribing things on a kind of a yearly basis, like birth control pills and so on. And that's not any different. So when I finish that discussion about the different treatment options, and then the patient comes to the selection that she wants to go ahead with, the medical treatment option, it's just really a simple prescription. I typically screen my patient for the high-risk factors. So there's really very limited, few contraindications for this new group of medication, and it's mainly because they have that little amount of estradiol that I told you about.

But because of that estradiol there are a few contraindications for that. One is patients who had DVT [deep vein thrombosis] or pulmonary embolism themselves, not family history. The other contraindication is the patient who have themselves had estrogen-dependent tumor, like estrogen-dependent breast cancer, and so on. And then the only other main contraindication is osteoporosis. But I've never seen a premenopausal patient with osteoporosis, extremely rare. But if you do see those patients, then they should not use either Oriahnn or Myfembree.

Other than that, it's really a very simple counseling session. I give them a prescription for 1 month with 11 refills, so I give them a 1-year supply. And then I counsel them to start the medication right away. Now ideally, if you look at the prescription, the FDA label for prescription you get the best result in your patient who starts the medication at the first day of their menstrual cycle.

And then I encourage them to use, say, in the case of Myfembree, just 1 tablet once a day, to use it the same time every day. Oriahnn is twice a day. So I just encourage them to use, like, 1 first thing in the morning and other one 12 hours later. And then that's it. It's a very

simple process.

Now, in terms of follow-up, I really don't ask the patient to come back until after 1 year, again, like many things we do in OB-GYN. However, I have this open communication with my patients. Most of my patients now use the portals and the patient portal at the University of Chicago; we call it MyChart. So they are welcome to send questions, etc. But I actually can tell you, very few patients actually send questions; they are really very simple medication to use.

Most of my patient with uterine fibroid, heavy menstrual bleeding, and other symptoms are very happy with the outcome.

Dr. Shulman:
Before we wrap up, Ayman, what's your 1 take-home message for our audience?

Dr. Al-Hendy:
A lot of patients with uterine fibroids suffer in silence at home because they think fibroid equals hysterectomy. By making this additional new information available, hopefully these patients will come out and seek medical help and hopefully take advantage of these simpler, newer treatment options.

Dr. Shulman:
For me, the take-home message actually goes back to an old metaphor, which is if you only have a hammer, everything is a nail. And for fibroids, as you just well stated, that hammer has been hysterectomy or myomectomy. It's been surgery. It behooves clinicians to get a second hammer into your collection. Because having an effective medical approach to symptomatic fibroids or fibroids impacting infertility is truly going to provide patients with better choices and ultimately with better clinical outcomes.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Al-Hendy, for sharing your experience and insight. It was great speaking with you today as it always is.

Dr. Al-Hendy:
Thank you so much, Lee, it’s always a pleasure to work with you.

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