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Misconceptions, Benefits, and Disadvantages of the Newer Oral GnRH Antagonists in the Management of Uterine Fibroids and Endometriosis

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Misconceptions, Benefits, and Disadvantages of the Newer Oral GnRH Antagonists in the Management of Uterine Fibroids and Endometriosis" is provided by Omnia Education.

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Dr. Shulman:
This is CME on ReachMD, and I'm Dr. Lee Shulman. Uterine fibroids and endometriosis continue to negatively impact many of our patients. Today, Dr. Ayman Al-Hendy and I will be discussing the place of GnRH antagonists in the medical management of both uterine fibroids and endometriosis.

Dr. Al-Hendy, welcome to the show.

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

Dr. Shulman:
Let's go ahead and dive right in. Dr. Al-Hendy, while surgery is often top of mind when discussing treatment options with patients seeking symptomatic relief from uterine fibroids and endometriosis, there is actually a strong reason to consider medical management first line. Why should surgery not always be our first choice?

Dr. Al-Hendy:
That's a great point. I think it's understandable why surgery has been and, to some extent, continues to be first choice for our colleagues and us when we're dealing with patient with benign gynecologies, such as endometriosis and fibroid, because for the longest time, and certainly during my training, that has been the case. Because really, there was no good, reliable, durable, efficacious, and safe medical treatment option that has been evaluated in high-quality, large, phase 3 clinical studies and FDA-approved or has achieved approval by other regulatory bodies in other parts of the world.

Now, in the last few years, we had these other viable alternative treatments – medical treatments. So I think it's time to change the paradigm a bit, and like any other medical condition that we teach our fellows and residents, and we ourself been taught when we were in medical school, any disease, we should always consider simple, medical, noninvasive treatment options. And only if those fail or the patient is not a good candidate for these options, then we can move to surgery.

Another important reason is almost all the surgeries we can offer have potential consequences, especially on infertility or potential fertility options. We know, for example, myomectomy most of the time – about 60% of time – leads to significant intraperitoneal adhesions. Hysterectomy, of course, will remove potential fertility options in the future. Also, most of endometriosis ablation surgery are

associated with challenges as far as adhesions, tubal blockage, and so on. That's why we should start to think about medical treatment options first as a first line of options for these patients.

Dr. Shulman:
I think, perhaps, the challenge for many of us gynecologists – yourself and myself included – is that we grew up in a time where surgical interventions really were the mainstay for the treatment of fibroids and endometriosis. But I think as we're going to be talking about today, we now have definitive and robust studies that show that those medical options clearly do provide relief for many women with symptomatic uterine fibroids and endometriosis.

Dr. Al-Hendy, can you tell us about what types of medical management are currently available for uterine fibroids and endometriosis? And what are the advantages and disadvantages of some of the more common options?

Dr. Al-Hendy:
Right. So things like NSAIDs, progesterone-containing products, such as progesterone IUDs or oral contraceptive pills with both estrogen and progesterone or progesterone alone, these are the usual options we use for both endometriosis patients and uterine fibroid patients. Uterine fibroids, of course, had a couple of other kind of unique products that we used to control the heavy menstrual bleeding associated with fibroid, such as tranexamic acid and aromatase inhibitor, although those have been used in very limited basis and really have never been thoroughly evaluated for fibroids. Also, this group of compounds called selective progesterone receptor modulator – basically the compounds that work as a progestin on the endometrium but as anti-progestin on the fibroid – has been developed and actually approved in other countries, in Europe, Canada, and other parts of the world. They have never achieved the approval in the US, and actually even in these other countries, now their use has been put on hold because of concern on liver injury. Now the most exciting group of compounds that came into this space were those working on GnRH signaling. Both GnRH agonists or GnRH analogues – we had this for longest time – and then more recently we have the GnRH antagonists.

Dr. Shulman:
You're absolutely correct. The expansive nature of options that are currently available really has been an impressive change over what had been nonsteroidals and hormonal contraceptives, none of which really demonstrated any consistent effectiveness or any long-term beneficial outcomes.

Let's now focus on those GnRH antagonists, as they do represent the most recent addition to our armamentarium. Can you specifically discuss their mechanism of action, the clinical data, and any real-world evidence that might exist?

Dr. Al-Hendy:
Absolutely. So these compounds are oral, because they are not peptide, so we can actually use them orally without worrying about them getting digested in the GI tract. So that's a major convenience factor for the patient. They are not injectable and so on, like the GnRH analogue or agonists we had before. The other very important thing about them, they go to the GnRH receptor in the anterior pituitary, binds to it right away, and inhibit it right away, so they start to work very quickly. What we had before – the GnRH agonists – they go to the same receptor, but they actually stimulate it first, because they are agonists. But they have been fabricated in such a way that they take the receptor inside the cell and not let go. So they stimulate the receptor, but because they don't let go, the receptor gets trapped in the cell and doesn't go back to the surface, so eventually they will inhibit this pathway. But initially, there will be this stimulation or what we recognize in our patient as flaring effect, and we used to tell our patient things will get worse before it gets better for like 2 weeks or so.

The GnRH antagonists, the new group, they bind, inhibit from the beginning. I think ourselves and our colleagues are very familiar with what happens after that. When you inhibit the GnRH receptor, then the anterior pituitary is not going to secrete the follicle-stimulating hormone and the luteinizing hormone. If you don't have FSH coming from the pituitary, the ovary is not going to be stimulated, so the ovary is not going to be activated, there's not going to be follicular genesis, and you're not going to have estrogen and progesterone production from the ovary.

Now, there are several members in this family. I'm going to kind of mention them in the chronological way, the way they have been developed and start to produce data – elagolix, relugolix, and linzagolix. So elagolix was the first member, and it has achieved FDA approval in summer 2020, and it has actually been approved before that for endometriosis. But there is a caveat here. So all of these compounds, because of the mechanism of action, they will actually bring the estrogen level in the serum very low, roughly to around maybe 20 or 30 picograms/mL. This is actually menopausal level of estrogen, and of course, we know what happens in menopause. So because we were developing these compounds as long-term durable treatment options, not just, you know, a few weeks or a few months, we had to address that. So the way the final product that's available in the market for prescription has been formulated to have the GnRH antagonist and also a little bit of estrogen and a little bit of progesterone. The little bit of estrogen in the form of 1 mg of estradiol is really to bring the serum estrogen level into this nice, therapeutic window, between roughly 30 to 50 picograms/mL. In that

nice window, you can avoid the side effects of low estrogen level and at the same time still not have enough estrogen to really make the fibroid and the endometriosis flourish and cause symptoms. So that's the target. So the way all of these compounds are formulated, and the 2 that has been FDA-approved, has the active compound and 1 mg of estradiol and then 0.5 mg of progesterone. The progesterone, of course, in the form of norethindrone acetate.

So, as I mentioned, elagolix was the first member of this family to achieve FDA approval for both endometriosis alone as elagolix alone and for fibroid as elagolix with this add-back therapy that I described. Now, with this formulation, based on the phase 3 clinical trials that we have completed and already published in *The New England Journal* in early 2020, have shown very high efficacy. So roughly around 75% – three-quarter is kind of easier way to remember – three-quarter of the patients responded by bringing their heavy menstrual bleeding back to the normal range. So basically, most of the patients achieved that in 6 months, and then when we followed the patients for another 6 months, this number goes actually to 90%. So 9 out of 10 patients who tried the elagolix with the add-back therapy have achieved a response in bringing their heavy menstrual bleeding back to the normal range.

Interestingly, very similar data also we have accomplished with relugolix with the add-back therapy. And the add-back therapy is exactly the same, by the way, in case of relugolix as well: 1 mg of estradiol and 0.5 mg of norethindrone acetate. Highly efficacious data – again, about three-quarter after 6 months, and most of the patients actually responded after a year. So relugolix with the combination therapy have accomplished that summer 2021, so fairly recently.

The only difference, I would say, between the 2 formulation – elagolix is approved as twice a day, so you take tablets, 1 in the morning – that's the one that actually has the add-back therapy – and then in the evening, you take elagolix alone; it's 300 mg per tablet. Relugolix is actually once a day – 40 mg of relugolix and then the add-back therapy in just one small tablet; you take it once a day.

The third member of this family is linzagolix. It is still going through the final evaluation and completing the data analysis and so on. For fibroid, it's a very similar formulation. It's the active compound, linzagolix, with the same add-back therapy once a day, and that's now under FDA evaluation for approval for fibroid. For endometriosis, it's just a little bit behind. It's completed a phase 2 study, and the data looks very encouraging.

Dr. Shulman:
Ayman, thank you so much for that comprehensive overview of the data and of these 3 options – 2 options and 1 still undergoing evaluation.

For those just tuning in, you're listening to CME on Reach MD. I'm Dr. Lee Shulman, and here with me today is Dr. Ayman Al-Hendy. Our focus is the place of GnRH antagonists in the medical management of uterine fibroids and endometriosis.

So when you're putting GnRH antagonists into practice, what adverse events do you most commonly see, and how do you manage these challenges in your patients with uterine fibroids or endometriosis? Further, how do you bring the patient into the medical therapy decision-making process?

Dr. Al-Hendy:
Excellent point. So because of what I described earlier, the add-back therapy, we really manage to mitigate and avoid most of the kind of expected adverse events because of the mechanism of action. So you still see things like hot flashes; it's actually very mild. As far as the final numbers about adverse events, hot flashes were about 20% in the elagolix arm and roughly around 10% in the placebo arm. In the relugolix study, it was about 6% in both arms, so – and again, in the few incidents that hot flashes happen, it was very mild.

We were looking at and evaluating the effect on the bone. So we did a DEXA scan during the studies at the baseline and also did that at 6 months and multiple timepoints after that, and we found actually very good stability of the bone mineral density. At 6 months, for example, in both elagolix and relugolix, there was no statistical difference between the arm that used elagolix or relugolix versus the placebo. Now, with longer-term use, we found some minimal, really clinically not significant difference in the treatment arm compared to the other arms. So overall, I feel the bone data was very reassuring. Just, we want to be aware that those who have already osteoporosis, if you have a premenopausal person with fibroid that has osteoporosis, they are not good candidate for these treatments.

Now, as far as choosing the patient for this medication, as I mentioned at the beginning of this conversation, in my mind, medical treatment for uterine fibroids or endometriosis really should be, like any other disease, should be the first line. That should be the first thing that comes to mind when we see patients with these conditions.

If they are not good candidates, or if they use these medications and somehow don't respond, which as I mentioned, very few number that you expect them not to respond, then we can move to more aggressive treatment. As far as contraindication, all the contraindications for estrogen that we are very familiar with as gynecologists comes into play here.

Dr. Shulman:

Dr. Al-Hendy, thank you so much for that deep dive into GnRH antagonists in the treatment of uterine fibroids and endometriosis. Is there anything else that you'd like our listeners to know that we haven't already touched upon in today's discussion?

Dr. Al-Hendy.
The only thing I would like to add is I would think there would be a paradigm shift in the field as there are many patients out there who actually don't want to have major surgery and prefer not to expose themselves to major surgery.

Dr. Shulman:
You know, those of us who are surgically inclined to view problems from a surgical viewpoint, and I think what we're seeing here with fibroids and endometriosis, as well as other gynecologic and even surgical conditions, is that that is no longer the paradigm. These medications, this must be the first-line, mainstream option.

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 joining me and sharing all of your valuable insights. It was great speaking with you today.

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

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