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Case in Point: The Use of GnRH Antagonists Pre- and/or Post-Surgery and the Potential Consequences of Repeat Surgery

Announcer:
Welcome to CME on ReachMD. This activity, titled “Case in Point: The Use of GnRH Antagonists Pre- and/or Post-Surgery and the Potential Consequences of Repeat Surgery” is provided by Omnia Education.

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Dr. Shulman:
Both medical therapy and surgery may play an important combined role during a woman's endometriosis journey. Today, we'll be joining a discussion between Dr. Ayman Al-Hendy and Dr. James Simon, in which they'll be providing insight into the value of using GnRH antagonists prior to and after surgery for endometriosis.

This is CME on ReachMD, and I'm Dr. Lee Shulman.

I'd like to first welcome Dr. Al-Hendy to our discussion today. Welcome, Ayman.

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

Dr. Shulman:
Great to be here with you as well. And in addition, from a studio near his home in Washington, DC, I'd like to welcome Dr. James Simon.

Dr. Simon:
Lee, it's really a pleasure to be here.

Dr. Shulman:
So let's get into our first question, Jim. Many women historically have undergone numerous surgeries for their endometriosis, but how successful are conservative and definitive surgeries in reducing endometriosis-related pain and other symptoms and in preventing disease recurrence? In a sense, how successful is surgery in managing endometriosis?

Dr. Simon:
Lee, that's actually a very good, but complicated, question. Let me take a stab at it. First, definitive surgery, that is to say, complete removal of the ovaries, tubes, uterus, etc., but at least bilateral oophorectomy, is very successful in treating endometriosis and its associated symptoms. But it means the end of that woman's fertility, and it means an instant surgical menopause with all the attendant symptoms and adverse consequences of the hypoestrogenic state. Endometriosis gone, but osteoporosis, pain, vasomotor symptoms, etc., present.

Less-definitive surgery is where the question really focuses. And I think it's a nuanced question. I don't believe that diagnostic

laparoscopy is required for endometriosis diagnosis anymore and should be reserved for experienced laparoscopic surgeons who can do deep pelvic endometriosis surgery with little or no consequence.

This subgroup of women with deep endometriosis are the ones that need surgery, but not definitive surgery, as I've mentioned. That surgery is very complicated, can frequently require urologic or gastrointestinal diversions and/or treatments, and that kind of surgery is beyond the expertise of most obstetrician-gynecologists, with the possible exception of gynecologic oncologists. So surgery is a special case requiring special expertise and not for novices. With that exception, I don't think there's a good place for surgery in the management of endometriosis, with specific exceptions, as I've mentioned, and unusual cases.

I'll give you an example. A patient that may not have terrible symptomatology but may have a partial bowel obstruction from constrictive or adhesive disease, she needs surgery. A woman who has terrible dyspareunia, deep dyspareunia, that needs deep endometriosis surgery regardless of any other symptomatology. But again, both those circumstances require a very experienced pelvic surgeon experienced with endometriosis to actually do the surgery.

So in conclusion, I'd say conservative surgery has little or no place in either the diagnosis or treatment of endometriosis, and it's only those special cases where surgery is indicated. But remember, definitive surgery, removal of the ovaries, still has a place in the management of endometriosis, with the provisos I've already mentioned.

Dr. Shulman:
Jim, that has been a great overview of this changing paradigm in the treatment of endometriosis as we really have segued from a surgery-based approach to a surgery and medical therapy approach.

So, Ayman, now let's move on to our other topic. Let's look at the medical interventions for endometriosis and its admixture with endometriosis surgery.

What evidence exists to consider using hormonal therapy, and notably GnRH antagonists as, first, neoadjuvant strategy prior to surgery, and, second, as an adjuvant strategy post surgery? And what would be their respective purposes in such strategies?

Dr. Al-Hendy:
This is a great question, a great point, Lee, because with these new tools that we have – as we know, we have now 2 new FDA-approved medications for medical therapy of endometriosis: relugolix combination therapy and elagolix as a monotherapy. With these new tools, we, as gynecologic surgeons and gynecologists in general and healthcare providers caring for women with endometriosis, we have a lot more tools to use, either independent of surgery or as an alternative to surgery, but also in conjunction with surgery, when the decision between the patient and her healthcare provider has been made to pursue with surgery. So in my answer to your question, I'm going to focus on the second scenario. What's the role of these medical therapies in conjunction with surgery?

So I personally, and the literature, support their use multiple scenarios. One is if the assessment of the patient, based on her disease burden, history, patient interest, and desires, and so on, the decision between her and her doctor has been made to do surgery, I think there's a very good role for this medication in that scenario. Once the patient consent to perform conservative surgery for endometriosis, for example, the pain doesn't just go away just because she signed the consent. She still probably have some waiting period until the time of surgery. For example, in my institution, it's probably around 2 or 3 months.

The patient will continue to have the symptoms, whether it's severe pelvic pain, heavy menstrual bleeding, etc., during that time, unless we help her with a medication.

So I have been successfully using these new options, the oral GnRH antagonists, as a pre-surgical preparation to give the patient relief of her symptoms and also to prepare her for surgery. And what do I mean by that? Many of endometriosis patients, because of the heavy menstrual bleeding, they have actually anemia, and of course we all like to take our patient to the OR with good hemoglobin, for example, at least 10 g/L, and in some instance we actually prefer 11 or higher to avoid the need for a blood transfusion, etc. So iron supplement, while it’s a good option, but it is typically associated with some side effects, GI side effects, and so on. So I have been using, for example, relugolix combination therapy, that the patient uses until the time of surgery to make her lose less blood. As you know, 70% of patients on relugolix combination therapy, for example, will enjoy amenorrhea very quickly after starting the treatment, or at least decrease their bleeding so to improve their hemoglobin level and correct their anemia.

I only ask them to stop the medication around a week before surgery to wash out the possible effect of estrogen, etc., before a major surgery. Also, I've been using this medication post surgery, post conservative treatment of endometriosis. As you know, even though we try to do the most comprehensive surgical management of endometriosis, there is still a chance of residual disease, and also the chance of recurrence is extremely high. Some studies put that at 70% after 5 years, especially in a younger population. So I've been using this medication also post surgery to decrease, or at least minimize, that chance of recurrence of endometriosis and recurrence of symptoms.

Now, that's the scenario. Another scenario is using this medication as a new adjuvant to treat endometriosis in conjunction with surgery. So what do I mean by that? In some cases, the extent of endometriosis disease is quite heavy, what you consider frozen pelvis or stage 4 based on the American Society of Reproductive Medicine. In those scenarios, sometimes, using surgery as the first line of treatment might not give the best results, so I've been using oral GnRH antagonists for about 3 to 6 months before these surgical procedures to minimize the burden of the disease so that when we do the surgery, the surgery is more effective and more likely to eradicate or ablate more lesions of the disease than if we had done surgery as the first intervention.

Also, I notice – and this is anecdotally. I really don't have literature on that yet, but hopefully with time. These are relatively new medications. I notice that using this medication before surgical treatment of endometriosis is associated with decreased blood loss during surgery. So using this medication in the context of a surgical intervention has many advantages. Of course, this medication also is a viable option as an alternative to surgery but maybe we'll cover that in another question.

Dr. Shulman:
Ayman, thanks so much. That was a great overview of your experience and the literature and how these new medications are being used to improve outcomes in women with endometriosis.

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. James Simon. They're just about to delve further into the use of GnRH antagonists with surgery during a woman's endometriosis journey.

Now let's turn to our third topic, use of GnRH antagonist therapy following a prior conservative surgery.

Jim, Alice is a 25-year-old woman who has recently relocated to your neck of the woods. She's in your office and indicates that she still suffers from endometrial-related pain following conservative surgery 3 months ago. Alice and her husband have one child 3 years of age, and Alice would like to consider another pregnancy in a few years.

Dr. Simon:
Lee, let's talk about this case because I see Alice, or her twin sister if you will, all the time. My first comment would be that with a 3-year-old and documented endometriosis, I might actually try and talk Alice and her husband into stepping up their desire to have another child rather than waiting. We know that endometriosis is a chronic and progressive disorder. And if they were lucky enough to have an uncomplicated pregnancy and delivery, I think there's no better time like the present with a three-year-old.

But that's partially a social judgment, but also partially a medical judgment. If it's just not a good time for them to have another child, I would warn Alice that delay, even if under treatment, might increase her risk of requiring assisted reproduction to get pregnant another time. And also might, even in spite of good therapy between now and the time of her next attempt at pregnancy, might require additional treatments with their own attendant complications, side effects, costs, etc. And we go through those one at a time. I'd focus on what are you going to use for contraception, Alice, between now and the time you plan to get pregnant again.

Those choices could be an intrauterine hormone-releasing contraceptive, which is known to reduce menstrual pain, even in endometriosis patients, with some minor benefits for endometriosis progression in a small subset of IUD users. Alternatively, continuous birth control pills, combined oral contraceptives, which seem to be better in endometriosis patients than cyclic use of oral contraceptives. It's a choice. Or the use of a GnRH antagonist with proper add-back to prevent ovulation, presumably prevent increase in her symptoms and progression of her endometriosis, but where we would additionally need to follow her bones to make sure that she wasn't losing too much bone and to make sure that she had adequate contraception while on those therapies.

Finally, I'd advise Alice to become pregnant sooner rather than later, regardless of her timing with her husband, and also to do so immediately upon discontinuing whatever therapy she's on so there isn't a long time span between her discontinuation of her contraception and her actual attempt to conceive.

Dr. Shulman:
Jim, this is not only an interesting case, but one I think that all of us see in our offices on a rather regular basis. So tell me, how does it all play out?

Dr. Simon:
So, Lee, let's imagine that Alice's pain is starting to come back in spite of my treatment for her, and it's about 16 months or so since I last saw her. She's thinking seriously about that pregnancy that we discussed previously. And while her pain is still reduced, it's slowly gotten worse over the past 2 months. My advice to her would be, "Are you sure you want to get pregnant now?" And if she says yes, to take her off her GnRH antagonist or any other therapy that she's been on, make sure that she's reestablished normal ovulatory cycles, provide her with non-narcotic pain medication because with endometriosis, she's going to have a recurrence of her dysmenorrhea.

That's probably acetaminophen or NSAIDs, if she's not pregnant, while on her menstrual cycle. And then I would encourage her to try very diligently with her husband, with whom she's been successful in the past, to get pregnant.

I don't believe additional surgery is required except as an emergency in some kind of adverse event. And I would also suggest that if she and her husband were not successful in conceiving, we'll call it, the old-fashioned way in about 6 months, to rapidly progress to some form of assisted reproduction because persistent attempts at pregnancy beyond 6 months frequently are unsuccessful, and each month that goes by, it's likely that her endometriosis and her associated pain is getting worse.

Dr. Shulman:
Jim, thanks again. This was incredibly helpful in really showing what is needed to take Alice and her endometriosis through to, hopefully, getting her that child that wants to have in the near future.

Ayman, it's important to consider the continuum of care when managing a woman's endometriosis life journey. in another case, we have a 21-year-old woman, married with no children. Her name is Nicole and her husband, Jim, have discussed Nicole's endometriosis diagnosis with you. Collectively, the decision is to start medical therapy, the objective being to control Nicole's pain, dysmenorrhea, and dyspareunia.

Dr. Al-Hendy:
Thank you, Lee. This is, as you can imagine, a very common patient scenario that I see in my practice, and I'm sure you and many others do that. This is a very young person, just really very early in her reproductive years, and unfortunately, she has the diagnosis of endometriosis. Using kind of the, I would say, the old paradigm of surgery first, this person or this patient will probably have her first laparoscopic ablation of endometriosis very soon at 21. Right away, considering the very high recurrence rate of endometriosis, as I mentioned earlier, about 70% in 5 years in some studies, we are setting this patient for a trajectory of multiple, multiple surgeries. By the time she's in her mid-30s, she probably had had 4 or 5 laparoscopies already. And we know these procedures, yes, they are minimally invasive, etc., but they are associated with possible risks and complications, such as adhesions, etc.

So I think medical treatment first is an excellent choice for Nicole and her family. So I would say, in this case, an oral GnRH antagonist would be a great choice for this particular patient. She doesn't have children, and from the scenario that she presented, doesn't plan to have pregnancy very soon. I think an oral GnRH antagonist would be an excellent choice to control her symptoms, dyspareunia, dysmenorrhea, and the noncyclic pelvic pain. It's a safe and effective and durable treatment that she can use long term and avoid this early surgical intervention. When and if she is planning to pursue pregnancy and build her family, she can stop the medication. The return of ovulation and hence the return of fertility is very quick after this medical treatment option, such as relugolix combination therapy, for example. Based on our withdrawal studies, the return of ovulation was within 4 to 6 weeks. So almost immediately, the next cycle after she stopped the oral medication, she will have her ovulation back and she will return, regain her baseline fertility, and she can pursue pregnancy, if that's what she desired.

Dr. Shulman:
You know, I think that return to ovulation of 4 to 6 weeks may be a surprise for some of our listeners. Actually, it's a little bit of a surprise to me. But I think it's important to understand that while she may be on long-term – or regardless of the term of medication usage, is that should she want to become pregnant, that the return to ovulation will be rather quickly and will, in fact, allow her to pursue her pregnancy desire in a rapid fashion.

That being said, she's back in your office and she actually is now 27 months – still very young, but still 27 months after you started her on long-term medical therapy, and she is now ready to try to conceive. And you talk to her about folic acid and the usual things. But what would be your counsel related to her therapy when she is preparing for pregnancy?

Dr. Al-Hendy:
That's an excellent point as well and a very common scenario. Like I said, once patient and her partner now decide to pursue pregnancy, in terms of the endometriosis, now she's been on the medication, on the oral GnRH antagonist for quite a while. I expect that the disease is in remission. I think we all know by now, and we need to emphasize, that endometriosis is a chronic disease. So our goal of these medical therapies, even surgery, is to eliminate the burden of the disease as much as possible, but it's not a cure. Unfortunately, endometriosis is a chronic disease that probably will continue until the age of menopause. And I share this with my patients when they ask about that.

So the disease is in remission now after 27 months of using oral GnRH antagonists. We can stop the medication. The return of ovulation is very fast. After that, they can pursue natural conception in the normal way. Now I'm assuming that they have completed a full workup. If infertility was a diagnosis in this scenario, they need to have completed their regular infertility workup. I think for our audience, no need to mention that the fact that female partner have endometriosis doesn't preclude that there could be other contributing factors such as

male factor infertility, etc. But if everything else has been worked up and is fine, and the only issue was the endometriosis, then by stopping the treatment, the disease is in remission, the return of ovulation is 4 to 6 weeks later, and then now she can pursue natural conception.

Dr. Shulman:
So let me ask you this question. She's ready to start to conceive. Would you do the infertility workup at that point, or would you wait for some time to see whether she could conceive or not?

Dr. Al-Hendy:
If they have not been trying, I mean, now we're going back to, you know, the basic approach to a potential infertile couple. So if her only issue was endometriosis, and from the beginning, if we look at the earlier scenario, they have not been pursuing pregnancy because they were focusing on Nicole's endometriosis. Then we need to actually do that workup. I would wait at least 6 weeks to the return of ovulation and return of normal hormonal production and then do the assessment at that time to really get a full, accurate assessment of all her workup. Again, I want to emphasize, also, evaluate the male factor contribution.

Dr. Shulman:
Absolutely. Okay, so now, 7 months after this, the workup has been unremarkable. No male factor, and she's back to ovulating after stopping the medication. But they're back in your office now and they have not been able to conceive, and they're having sex on a regular basis, etc. She relates that her endometriosis pain symptoms have started to return after they had been really mostly muted for the time that she's been on the medication. What do you tell them?

Dr. Al-Hendy:
Right. So that's also, unfortunately, is potentially a common scenario in some cases. Now we go into the discussion about the different options. I don't think we are at the point that the literature suggests one option at this point. So one option is to consider surgical intervention for endometriosis, because then, after the surgical ablation of endometriosis, then they can immediately pursue pregnancy after that with no delay. Another option is to then consider an infertility referral to the reproductive endocrinologist and infertility specialist and to consider artificial, you know, reproductive techniques. Most of the time, this scenario, I would start with simple intervention, such as ovulation stimulation, IUI [intrauterine insemination], but then, also, we can discuss the other options.

Dr. Shulman:
Ayman, that is a great discussion on , again, a very common issue in women and in couples who unfortunately have to deal with endometriosis.

Jim, I'm sorry you couldn't be here today, but I wanted to thank you for participating. It's been wonderful having you here today.

Dr. Simon:
It's a real pleasure to have been part of this podcast, Lee and Ayman. Thanks for having me.

Dr. Shulman:
And, Ayman, thanks for being here today. It was great doing this program with you.

Dr. Al-Hendy:
A pleasure.

Dr. Shulman:
Unfortunately, that's all the time we have today, so I want to thank our audience for being here today and to thank, again, Dr. Simon and Dr. Al-Hendy for sharing your experience and insights. It was great speaking with you today. Have a wonderful rest of the day.

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