Transcript Details

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Optimizing Medical Management of Uterine Fibroids: Achieving Patient-Centered Goals and Outcomes

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Optimizing Medical Management of Uterine Fibroids: Achieving Patient-Centered Goals and Outcomes" was presented during Omnia Education's Women's Health 2021: Beyond the Annual Visit.

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Dr. Nelson:
Hello everyone, I want to welcome you to this session on Optimizing Medical Management of Uterine Fibroids: Achieving Patient-Centered Goals and Outcomes. I'm Anita Nelson, and I'm happy to give this good news talk about some advancements that have been made in a treatment of a problem that has been bewildering and frustrating women and clinicians for such a very long time. I do have potential conflicts of interest, and hope that they do not bias any of the information that I'm providing you today.

So what are we going to be doing together? Well, we want to help you recognize the role of early diagnosis and culturally sensitive care in improving the outcome of patients who do have uterine fibroids. We want to formulate strategies to engage patients in discussions about their fibroid symptoms and about their preferences for different therapies. And we want to evaluate the latest evidence on the mechanisms of action, safety, and efficacy of this new class of drugs that we have at our disposal now to help women: GnRH antagonists for the management of fibroids, particularly heavy menstrual bleeding due to uterine fibroids. I think you know that these are almost ubiquitous, right? That leiomyoma are the most common uterine neoplasms and that over the lifetime risk women face somewhere between a 70% and a 80% chance of developing a fibroid. We know the estimates of the prevalence really vary depending upon how it's established. If you ask women, "Do you have fibroids?" as opposed to you just pull up people and do ultrasounds on them, and you can find the asymptomatic little fibroids that are resting somewhere in the fundus and not bothering her at all. But we have seen that there are consistent patterns across all these different kinds of studies. We do know that the prevalence of leiomyoma increases during the reproductive years. We clearly know that Black women have higher rates of these benign lesions than White women do and that we know that somewhere between 25% and 50% of women who have fibroids have symptoms that are attributable to those growths. But there are often significant delays in making the diagnosis of those fibroids. And we can see that there are significant adverse impacts on the health and the quality of life of women with fibroids. And annual cost estimates in the United States run in the billions of dollars. And one of the measures that people have been looking at is that there's been a substantial increase in the number of ED visits as a result of fibroids, that women are turning much more in the acute time frame, right when they're bleeding acutely, as opposed to being seen and having it diagnosed and treated maybe at an earlier time. So all these things coming together really make it a really high priority for us to really investigate and to try to help women who have these.

Now there's some fascinating facts about fibroids. We know that every single fibroid that is out there is actually monoclonal. That means every single cell in that fibroid is an exact duplicate of all the other cells that are in that fibroid, that women certainly can be totally asymptomatic from their fibroids. But we also know that fibroids can cause life threatening bleeding, it can cause excruciating pain, it can be responsible for infertility and for pregnancy loss, and that there are so many different variables that interact to help explain these

different impacts. The location of the fibroid can be important, how large is it, how many of them, does she have scattered, and in what size and what, locations. We know that some of these fibroids can be massive; they can invade into other structures. I know they're benign, but they have all of these abilities that can seriously impact on a woman's health. And again, we're coming to understand that there are both genetic and environmental factors that can trigger the formation of these tumors and also dictate its growth. Now, what's really intriguing about this is if you know what turns it on, then that gives us a target for preventing or controlling the growth of the fibroid itself. And another fascinating and encouraging fact is that we do have a growing number of treatment options. There's still limited, to be honest with you, but it is nice to know that people are actually looking into this very common problem and developing innovative ways to help treat it and particularly the consequences of it.

We've known for years that there is an estrogen dependence on the of this fibroid not only in its development, but its progression. But it's kind of interesting. The supporting evidence is very clear, right? These don't appear – they're very, very rare – before puberty, they tend to shrink, not always, but they can shrink after menopause when she loses her estrogen. They certainly flourish in pregnancy when there's huge amounts of estrogen around. We know that estrogen and progesterone receptors are found in much higher concentration in the myometrial cells of the fibroid than they are in normal myometrial cells. We know that smokers, remember smokers metabolize their estrogen faster, they have a lower incidence of myoma, oh you don't want to say that out loud, do you? You don't want to do anything to support smoking. But it does give us evidence there. And that we know if we give GnRH agonists over time, that this will result in the reduction of the myometrial volume. The only thing that's a little puzzling to us is that many women, many women have very small fibroids that just don't grow. So is there something different about those fibroids than it is those that do progress? And I bet you the answer is going to be yes. It's not all just about estrogen. But estrogen has a huge leverage on the impacts of the fibroid that women have.

What are the risk factors? These are the things, each one of these things doubles the risk of the patient having it, her ethnicity, particularly Black ethnicity. As we said, it progresses as women age. Grows a lot in perimenopause because she has unopposed estrogen. We know that women with hypertension, certainly a family history of fibroids puts you at a higher risk, food additives, soy milk consumption – there've been all kinds of things that people have looked at and found high association. We also know that there's some protective factors. In older women, use of oral contraceptives, Depo – both reduce the risk of fibroids and treat the manifestations of it. There is some data that younger women near the time of menarche, if they take estrogen-containing pills, might be at slightly higher risk for developing leiomyoma. We said smoking with low BMI and parity can all be protective factors, but we don't want women to have children so they don't have fibroids, right? We want to have something else.

The natural history of leiomyoma is kind of bizarre in some situations and puzzling in others, that we know that these can grow into very large sizes that fill the pelvis and compress all the other organs that are there. The average growth rate, and who's to calculate this, is about 1.2 cm in 2.5 years; that was interesting. But some of them shrunk by a centimeter and some of them grew by almost 7 cm in just 2.5 years. We know that these tumors can outgrow their blood supply; we see data in pregnancy don't we? And they'll degenerate and undergo terribly painful necrosis. They will generally shrink without estrogen, and that's why we turn to the postmenopausal women, but unfortunately that's not always reliable. But they will at least slow their growth after the loss of estrogen.

We've been very lucky to have this wonderful new system introduced from FIGO [International Federation of Gynecology and Obstetrics] where we actually get a subclassification system that was really designed to mimic the FIGO staging systems from the cancers. And so we'll see that there's some mucosal, you can see each of them is numbered, and we have definitions for each of the different types that we have so we can more effectively communicate with each other. So 4, the fibroid is totally encased; it's an intramural. If it extends into the endometrium by less than 50%, then we call it submucosal and we number it a 1. But there are hybrids, right? We, we know that leiomyoma can have different sorts of relationships. We know that the hybrid leiomyomas that can impact on both the endometrium and the serosa crossing all of those certainly can have differential impacts altogether. We know that the ones that protrude, they all started in the endometrium, and they either grow inside the cavity, become submucosal, and some of them don't know any limits, they actually fill into the cavity itself. Some of them will develop a pedicle and actually deliver through the cervix, we call that an aborting or a prolapsing fibroid. And I've had patients come in, huge amounts of bleeding, terrible cramping, it's like she's delivering a baby and you look in there and there's this huge fibroid that's literally being contracted down by the uterus, trying to rid itself of it, but inverting itself as it does that and causing even heavier bleeding. We know that it can grow to be outside on the serosa and become, again, pedunculated on a long stalk, and that can actually torse and we can have necrosis that way. Or it can break off and establish a new blood supply from another organ. We can get the broad ligament leiomyoma and we can translate those into the new terminologies that we have. We know that it can invade into the IVC [inferior vena cava] and become – fill that venous structure with leiomyoma and that can be deadly, right, to have this.

But what are the common clinical presentations for women who have symptoms from uterine – heavy menstrual bleeding? You've got to keep, that's very, very important and with it comes dysmenorrhea and pelvic pain. She may have because of pressure sensations just

like she gets with pregnancy, urinary problems, either retention or frequency. You can get compression of the bowel to the point where she suffers constipation, if these are in the areas where there could be implantation, infertility problems or recurrent pregnancy losses can happen. And in areas where there are adhesion formations or just mass effects, maybe dyspareunia. On the OB side, depending upon the size of these, lower birth weight fetuses could be there, short cervix certainly could be there and predispose her to preterm labor.

But we really want to focus on the heavy menstrual bleeding due to uterine leiomyoma, and these, again, are very common. In a US survey, almost three-quarters of women who had self-reported fibroids reported that they had heavy menstrual bleeding, and nearly half of those said that they had a passage of clots and needed to use more than one form of protection at a time. And look at this – over two-thirds had anemia or fatigue. International surveys support the same findings, right? Heavy menstrual bleeding, prolonged bleeding. So we know that a number one consequence of symptomatic uterine fibroids is this heavy menstrual bleeding. And I, I think we need to remember that anemia is the number one cause of years lived with disability in women. And this is true around the world. And we see how frequently the women who have severe anemia, that it's due to fibroids. In the study that we did, 47% of women who were hospitalized with a hemoglobin of less than 5 due to heavy menstrual bleeding, the cause was found to be fibroids. So, amazing. And of course, there's a huge impact, deleterious impact on quality of life and a woman's productivity.

What other impacts do we see? Well, again, the fibroids are associated with a disability that is similar to other chronic diseases. There's lower vitality and less social functioning than women who have breast cancer; that's how debilitating it is. We know that the impact on GYN practice – how many women undergo hysterectomies every year because of fibroid-related problems? And we know that the lifetime risk of hysterectomy in the United States is 45%, and to realize that nearly half of that was due to fibroids and the problems they caused really make this a high-priority item.

But as we mentioned, women who are symptomatic with uterine fibroids have impacts, really negative impacts on their emotional well-being, that we see that nearly 6 in 10 reports feeling sad or hopeless, you know, 7 in 10 uneasy about the physical presence of the fibroids, and they really worry about bleeding and soiling their clothes, their bedding; they can't sit on certain couches or chairs during that time of the month. This really makes a woman feel very isolated and very unsure.

So when we're seeing the women here, we want to get the history, we want to know about her uterine bleeding patterns that she's having. Does she have iron deficiency anemia? Are there pressure symptoms? Does she have a history of fertility challenges? And does she have acute pelvic pain or maybe pressure sensations that she's interpreting as pain? And on physical exam, we really, really want to do a good pelvic exam. We want to be able to map out as much of this irregularly contoured uterus as we can.

We can turn to diagnostic imaging. We know that transvaginal ultrasound is a rapid and cost-effective way to evaluate uterine fibroids. But sometimes the count gets so high and the acoustic shadowing can certainly obscure some of the fibroids that we have, and we can see that the positive predictive value of diagnosing endometrial cavity distortion can be as low as 47%. We know that if we can routinely order saline infusion sonography, certainly improves the ability to see those distortions and those intracavitary lesions. Hysteroscopy can also improve it. 3D ultrasound is very good. But still today, MRI is the most useful for mapping the location, size, and anatomical relationship of fibroids, and this is a tool that we really rely on. Still, when we're talking about myomectomy, will she have enough uterus to put back together again after we shell out all the fibroids that she has? And sometimes you just have to sit back in awe of the, the massiveness of the lesions that you do find and of the woman who lives with these and how it's impacting on everything in her abdominal cavity. And when you actually retrieve these things and you see the vascular supply, that almost looks like a malignancy; it's so highly vascularized.

We have an array of surgical options to offer women, and the tendency in surgery has become less invasive, and so we appreciate that particularly for women who want to maintain their uterus. We can destroy the endometrium with ablation with a wide range of techniques. We can do myomectomy with a wide range of invasive and more at distance techniques today. We can destroy the myoma, embolize it. We can do MRI-guided, focused ultrasound, again, trying to destroy it and to shrink it. Cryoablation, but the final cure is going to be hysterectomy. But all of these options again should be on the list that we discuss for women who are interested in dealing with their heavy menstrual bleeding with surgical options.

But what do we really want to consider when we're talking about the treatment options for heavy menstrual bleeding with uterine fibroids? We really want to find out from her what are her desires for fertility? How much does she want? How strong is her desire to retain her uterus or what they call uterine preservation? And then of course, we need to know the inventory, right? What's the size, location, and sites of the number of the fibroids that she has? What are the symptoms caused and can we relate some of those fibroids to those symptoms? If we got rid of this fibroid here, would that be enough, right? Is there some way, middle ground that we have? And clearly what is the intensity of the impacts of the fibroids on the woman's health and her quality of life? Very important in this equation, pivotal in this equation is the patient preference. Sometimes I will agree with you patients want things that we can't deliver,

and sometimes we'll just do our very best to meet their preferences and then they can learn for themselves that this treatment that they sought may not be effective enough, or they may find ways to make it work. But again, it's her body, her preference. And we have to always, in managed care, in today's environment, deeply consider the cost-effectiveness of different therapies. We don't want to ring up a whole bunch of cost for very little value to the patient or to the healthcare system.

So shared decision-making is so central when dealing with the problems that are caused by uterine fibroids and particularly when we're talking about having heavy menstrual bleeding. So in general, we want to follow those standard recommendations that we want to listen to the patient attentively. I like the analogy of the Doppler. We send out a little bit of message and it's so much more productive if we just sit there and listen to what bounces back to us. We get insights that we could never understand, this nuances of the way she views her disease and whether she's willing to trust us, to trust our recommendations, what it is she brings into the room with her from her dalliances with the social media, all of those are very important. Developing their relationship of trust and teamwork and having her as a partner is very important, have her feel valued and that we are listening to her. Decision aids can be helpful here. And then as we're running through the risks and the benefits, certainly assess what her expectations and her goals are and see whether we can achieve them with the therapies that we have today. And we don't want to just say, "The guidelines say women with fibroids should be given." We want to personalize that, right? "It sounds to me as if your problem is and we have these options that we can offer you." And then certainly we want to factor in the severity and her desires for fertility and, as we said, the others. And find out what her fears are. And when we're considering medical therapies, does this seem safe to her? She may have questions about long-term effects. We know that hormones leave the system like this, but she doesn't, right? And the support that she has from her peers, what has she heard, and how can she answer their concerns when they come up? And very importantly, what are the impacts of the short- and long-term impacts of heavy menstrual bleeding on her health and on her fertility goals? And how easy is it for her to use the therapies that we're suggesting?

So maybe we can deal with a, a case. A 30-year-old nulliparous woman from the African diaspora presents with heavy menstrual bleeding for 6 years. Now, an important thing in her history is her mother had an early hysterectomy. Now, she personally has required transfusions because of her heavy bleeding and her anemia that results. She tried hormonal contraceptives, but with very little effect, and she was told she needed a hysterectomy. But she honestly doesn't understand why something that isn't cancer really needs such drastic surgery. She saw what her mother went through and unfortunately, mother did have complications from her hysterectomy and did not feel that she had had a chance to have the family that she had always wanted. So that put pressure onto your patient. So you see the intergenerational issues that are there. And I think it is important to understand that fibroids in Black and White are not always the same. We know that 25% of Black women will suffer from fibroids by the age of 25, and 80% of them will have them by the end of their reproductive years. And we know that Black women suffer from fibroids 2 to 3 times more. So it's not just having the fibroids, but it is suffering from them, being symptomatic, right? And clinically relevant fibroids are detected in about 35% of White and 50% of Black perimenopausal women. And study after study validates the fact that Black women experience more severe disease, either bigger fibroids, longer bleeding, greater likelihood of surgery, larger masses, compared to any other group, particularly compared to Caucasian women. And because of all of these experiences that women have, because they have gotten to a really extreme position where the only solution is surgical, that actually boomerangs and actually may result in a delay in her care.

So again, our counseling points, I think it's always important to listen to her frustrations. I think you'll be really surprised to hear what she's been through. What are her fears? Why is it that she is reluctant? What has she heard about things? What workup has she already had? If she's a new patient, why does she have to have the same tests done again and again if we can get results? And if we can't get those results, then maybe she can understand why we want to duplicate the tests but we don't want to make her feel like a ping pong ball in the middle of all of this. And again, clarifying her goals, both short term and long term, and getting to her point. Why does she think that the earlier methods didn't work? And one thing I've learned over the years is that, again, it's often due to a misunderstanding of what we're offering her as a treatment when she sees it as a cure. And this happens often with bleeding. I've had patients myself who I took care of them because of excessive bleeding, put them on birth control pills, and boy it did its work, right? It really was very, very helpful, very effective. But what happened to her was as soon as she stopped the pills, the bleeding, abnormal bleeding returned, and she thought the treatment was a failure. So ask her, what was your bleeding like when you were on the pills, right? And then have her understand this difference between the treatment and cure as a goal, overall.

But I think we have to be humble, that there are studies like this really good one that just came out a few years ago that queried women who are being treated right now for uterine fibroids. What were the symptoms that they had? What was the prevalence of the symptoms? And you can see here that over half of women has constipation, bloating, and diarrhea when they were on the therapy. 50% had, still had persistence of heavy menstrual bleeding. It may be less than it was before, but it was still excessive. They had pelvic pressure; they had passage of clots. Not only was their bleeding heavy, but they're still passing clots, and some of them – a third of them were still having intermenstrual bleeding. So we know – we all know women who have fibroids for whom the current options just

don't match their preferences and aren't achieving the goals that we would want them to have. So clearly, it has been recognized for quite some time that new medical options are needed.

Case 2 is another classic one. Here's a 45-year-old White woman with heavy menstrual bleeding, bulky uterine fibroids who, for some reason, wants uterine preservation. It's kind of interesting. I've heard this; I'm sure you have: I don't want to be a statistic, right. New things are happening all the time. Why can't I just wait it out until menopause? She's only 45, she's got several years to develop some significant anemia, especially when you layer over her heavy menstrual bleeding now the impending anovulatory cycling that happens quite often in perimenopause. So you really do worry. If her only problem is the bulky uterine fibroid and she's willing to live with the pressure sensations that she has, but when it's linked to having menstrual bleeding, that's going to really be deleterious to her health. So why is it that women are hesitant, and we already talked about some of the mental health issues here, but these I think are kind of interesting when women are asked what they worry about with the fibroids. They're worried about health complications from them. And some of these are legit, right? The anemia that we talked about, the impact on the quality of her life. But if she thinks that this is a precursor to cancer, we can assuage her fears. Or that it's going to lead to – and I'm sure you've heard those stories that have terrified women about these benign structures in her uterus. Most do fear future fibroid growth, and that may be legitimate. But look at that: half of them fear the need for hysterectomy. And look at that: a similar number, as I said, fear cancer from it.

So reviewing what our medical treatment options are for heavy menstrual bleeding associated with uterine fibroids, and in many other sources, too, we know that NSAIDs certainly are very helpful. They adjust the prostaglandin balance and help control the bleeding, and we can say for women who have idiopathic bleeding, that they can reduce bleeding by about 20% or 30% and that may be enough, right? And it's given episodically so she doesn't have to be on something all the time. Antifibrinolytics can be helpful, particularly for women who form those blood clots at the end of the cycle, but then lyse them, and she has to form them and form them and form them. We don't have to prove that she has this as a problem. People are using this agent a lot more liberally these days to help with heavy menstrual bleeding. Combined hormonal contraceptives certainly are first-line therapy, but we often turn to progestin-only contraceptives, and in less frequency we've used GnRH agonists because it is very limited, 6 month time. Usually this is a bridge to surgery or to some other therapy. And what we're very excited about is the new guy on the block, the GnRH antagonist. And then in the future, maybe we'll be able to use in this country, as they are in Europe, selective progesterone receptor modulators like ulipristal acetate and an increasing role for aromatase inhibitors.

But I thought this one might be interesting, and this was a retrospective analysis that a large commercially insured group of women – over 40,000 women who had heavy menstrual bleeding from fibroids from the turn of the century for the first – more than a dozen years. And number one therapy was the short-acting combined hormonal contraceptives: the pills, the patch, and the rings. There has been an increase in the utilization of LARCs since 2013, but not necessarily because of fibroids. People are sometimes hesitant because of the distortion in the uterine cavity. An equal number of people were using GnRH agonists – analogs, pardon me, and then we had a minority of them using the, the antifibrinolytics.

Well, turning to the literature, we're kind of on waffly grounds to be honest with you. We use, as our first-line therapy, combined oral contraceptives with not that many studies to support it. Certainly we know that the COCs don't work quite as well as the LNG-IUS, if she's a candidate for the LNG-IUS. But certainly their conclusion that evidence regarding the use of COCs as treatment for women with symptomatic fibroids is very scarce and of low quality, and we are very uncertain about the real efficacy of such treatment. But we know analyses notwithstanding, this is where we turn to for first-line therapy for many different reasons.

What about DMPA? Now read the fine zone here. They're giving traditional 150-mg injections every month for 6 months. And at 6 months, they only have a 30% amenorrhea rate and 70% improved bleeding. 15% had an increase in hemoglobin, and there was a substantial decrease in mean uterine volume. But that's not your everyday contraceptive dosing. And we can certainly find somewhere room in between. If our goal is to help control the endometrium, maybe a priming with GnRH, get the amenorrhea, and move on to the injectable progestins. But by itself we're not going to generally use this. But this is one of the only studies that really is specific for the treatment of DMPA for HMB with fibroids. Obviously clinical practice is not as well studied as in these studies.

A systematic review of the LNG-IUS in women with uterine fibroids in women who met the criteria. And in general, that means that the fibroid is less than 4 cm, not distorting the uterus – uterine cavity, and less than 50% of the fibroid is in the endometrial cavity itself. What we found is that blood loss did decrease among LGN-IUS users who were able to continue till the end of the study, and all the parameters that we wanted to see that represent less bleeding and less anemia certainly were demonstrated by this study. But we did find that there was a higher expulsion rate, up to 11%, but that meant 89% of women got to hold onto it. And expulsion was related more to uterine fibroid size than it was to location.

We have relied on GnRH agonists usually preoperatively to shrink a fibroid, not necessarily for doing myomectomy, but if it made a difference, maybe she could – if it got shrunk down enough, maybe she could have a vaginal hysterectomy as opposed to a

laparotomy. SERMs are not used in the Unites States for this purpose, although they are used extensively, again, in Europe because there's still remaining questions about hepatic toxicity that have not been resolved at the FDA.

But what is new? What we can be talking about today with patients that we didn't have available to us just a year ago was this whole new class of drugs, the GnRH antagonists. These things that we thought about in the '60s, actually, for contraception are actually coming back now for heavy menstrual bleeding and, as we'll see later on today, for the treatment of endometriosis. And what is special about these are not only are they effective, but they have very rapid onset, as opposed to the agonists where you have that actual increase in bleeding before you have a decrease in the stimulation of the pituitary. So where we sit today is with 2 FDA-approved agents, elagolix and relugolix, and in clinical trials there is as third agent that we'll talk about.

Well, let's start with the first one. Elagolix, its overview, it's an oral non-peptide GnRH antagonist. So what it does is it binds to the receptors for the GnRH on the pituitary, so it keeps that organ from hearing the GnRH stimulation that happens. And so what that's going to do is, very rapidly, within 24 hours of ingestion, you're going to see the, gonadotropins dropping, so she's not going to have FSH going to the ovaries saying make follicles that make estrogen. And when that shuts down, the ovarian sex hormone production shuts down, then what you see is that there's a lack of stimulation of those estrogen, the estrogen from the ovary to the endometrium, so that stops the proliferation of the endometrium and therefore blocks anything that needs to be sloughed at the end of the month. Now this is being formulated with a low-dose steroidal add-back condition, so it's actually a combination drug that's been put together to limit – to be effective in shutting down the pituitary stimulation of the ovaries, to put the ovary to sleep, but also to keep – since there is not going to be estrogen from the ovary, we don't want the woman to go through a lot of menopausal problems. And so there will be estrogen and progestin add-back to protect the bone, to try to protect the endometrium. And of course, if you're giving estrogen to help protect all of those symptoms of hypoestrogenism that comes from shutting down the ovary, then if she has a uterus, and of course she does, then you add the progestin so you don't have unopposed estrogen that could lead to hyperstimulation.

Well, how well did this work? And these were the 2 studies that we want to look at, and I think it's important for us – in every one of the studies for heavy menstrual bleeding, the FDA sets a very, very high standard for success. And what that means is that you measure the baseline bleeding, and every woman coming into the trial has to have excessive bleeding. Usually, you have to demonstrate 2 episodes, consecutive episodes of bleeding, more than 80 mL of blood, not just fluid, but blood itself. And then she can be enrolled in this study. Clearly they ruled out any other cause of heavy menstrual bleeding before the women could come in. So these were uterine fibroid-associated heavy menstrual bleeding. And what you do is you give the therapy and you measure the impact at the end of the study on the blood loss, and there are generally 2 standards that have to be met. Number one, she has to normalize. So whatever level she started at, she has to bring her blood loss down to less than 80 mL, and she has to reduce her blood loss by at least 50%. Now that is a very stringent criteria, because if we think about it for just a minute, what if a woman were to lose 320 mL every single month, right? And we brought her down to 90 mL, well that meets the 50% requirement, but it misses the 80 mL maximum. So that woman, even though she had that remarkable reduction in blood loss and she's probably very, very happy with it, is a failure because she didn't meet both of them. And I bet you can figure the other one, where she doesn't meet the 50% but she is normalized. But when you have this, so really recognize how very stringent these requirements are and look at the results of this study here, where in the light pink or purple/violet, we see the placebo has minimal effect. When you gain elagolix alone and that's the, the heart of it, that's the antagonist that's going to shut down the whole system, that we can see that the that 85% or 84% of women met both criteria. Now, if you gave elagolix with the add-back therapy, so that you protected her from the menopausal symptoms and impacts on her body, then it was the 68%. If we look at the second study that was the same sort of design and good distribution of representative people, we can see that the add-back didn't have as negative an impact, that both arms were about 77% success rate, and that's very high. Any of those numbers is very good, but it's good to see overall how very effective this method was.

What else we have is relugolix combination therapy, and again, it's an orally active non-peptide GnRH receptor antagonist. It's suitable for daily use, and it's a once-a-day oral as opposed to twice a day. It competitively binds, just as we talked about, and it's given with relugolix, the antagonist, and it's combined also with estradiol and norethindrone acetate to try to get that whole-woman approach so that we can take away her problem from heavy menstrual bleeding but not induce a lot of other problems like strong osteoporosis and hot flashes. So again, it's efficacy in women with heavy menstrual bleeding to avoid the hypoestrogenic. How well did this one work? Same story here. The design was just slightly different. They gave women, for the first 12 weeks, relugolix only and then for the next 12 weeks, they added in the add-back, and that's the teal color there, as opposed to the women that got the combination drug for the whole time. And you can see that in both trials, there is substantial responsiveness. So with or without the estrogen add-back and for long-term use, we don't want women to go through all those symptoms that both of these new therapies, based on an antagonist rather than an agonist have very rapid onset and are very highly effective altogether.

There is another one that that's under trial right now; linzagolix, okay? It's in late-stage clinical development, again, for this same indication, and it's going to be adding a high dose with estrogen add-back and comparing it to a low dose without add-back. And it's

being assessed for long-term treatment for women with add-back therapy contraindications. So if she can't use estrogen for some other reason, then only the lower dose antagonist can be effective for her. And here are some of the results that you can see, and we can see that the higher dose therapy with add-back was more effective, and the pooled analysis, but to have a 50% response rate, a success rate for patients who can't take estrogen, I think that creates another niche and option for us to consider, to have on our list.

All right. Well, clearly we're very excited about this new therapy and to have a new tool in our toolbox, if you will, and for women who develop progestin resistance to our therapy, right, our progestin-based therapy, to be able to offer 24-month therapy with strong continuation rates, all of those are such exciting properties for these therapies that we want to get back and talk to patients about these and add one more thing to our list. And sometimes the medical therapies we have are going to be shorter life, maybe 24 months limitation for some of these newer therapies, but that gives a chance for the patient to recover, to improve her symptoms and, you know, even if she's just trying it short term, decide if this works for her or not. And it gives her time to consider her other alternatives, and we can use these new medical therapies as we have other medical therapies in the past to bridge from one treatment modality to another while we're improving her quality of life, maybe working on her comorbidities, and making it possible for her to have continued good health altogether.

So where are we today? I think in summary, fibroids clearly are a common cause of heavy, prolonged menstrual bleeding that can have very serious health impacts and significantly reduce people's quality of life. We know that the traditional medical therapy can offer some relief, right, with NSAIDs, antifibrinolytics, combined hormonal contraceptives, progestin-only contraceptives, androgens, and the GnRH agonist. But the newer approaches, especially the oral GnRH antagonist, offer distinct benefits of rapid onset, efficacy, good tolerability, and high acceptability. So, again, we're glad to celebrate the introduction of this whole new class of options for us, and I think you'll be pleased to see, in another lecture that follows, that there are other applications for this wonderful new fast-acting oral therapy. So I want to thank you very much for your attention and look forward to your questions.

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