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Individualizing Management of Endometriosis Pain: Current Evidence, Potential New Strategies, and Ongoing Research

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Individualizing Management of Endometriosis Pain: Current Evidence, Potential New Strategies, and Ongoing Research” 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 of really good news on Individualizing Management Of Endometriosis Pain: Current Evidence, Potential New Strategies, and Ongoing Research. As I said, this is an exciting time for so many topics in women’s care where we’re actually beginning to see progress. My name’s Anita Nelson, and as you can see, I’m currently Professor and Chair of Obstetrics and Gynecology at Western University of Health Sciences. I do have potential conflicts of interest, I hope that none of them emerges in this talk, but please realize I’m not intending to have any bias in the information that we share.

What we’re going to be doing in the next couple of minutes is identifying clinical practices that can support the accurate and timely diagnosis of endometriosis. Believe it or not, things have changed there, too. We want you to be able to assess the benefits and challenges of various medical therapies for initial and ongoing care of women who have endometriosis. And we want you to be able to evaluate the recent clinical and real-world data about medical management of endometriosis.

So from that kind of an overview, let’s dive right in.

I think everyone recognizes that endometriosis is a chronic inflammatory disorder that substantially reduces women’s quality of life. Technically we know on histology, that what we’re looking at is the ectopic presence of both the glandular and the stromal endometrial tissue, so it’s just outside the endometrium. And usually they want to see hemosiderin-laden macrophages to really knock down and to confirm the diagnosis. Now what’s really interesting is even though these are endometrial tissue explants, if you will, they have differences with the molecular structures of the cells that are actually found in the endometrium. So normal endometrium does differ from these endometriotic implants that we find elsewhere. And we come to understand over the last several years that this just isn’t squeezing out that tissue during the menses or other things, but the presence and the growth progression or regression of this disease is really strongly influenced by genetic, environmental, inflammatory, immunologic, and even angiogenic factors, and certainly, epidemiology plays an important role. And what’s really interesting is that now we’re even finding that the microbiome is implicated not only in the vagina but in the bowel. So fascinating progress for looking at this condition from so many different vantage points and seeing different places where there can be intervention short term and long term. So this kind of investment in really getting down to the nitty gritty of endometriosis is really going to be paying off, I think, in the coming years.

And this is so important because we have recent estimates that shows that endometriosis affects about 1 in 10 reproductive-age women. And if you add them all up, that’s 190 million women worldwide suffer from endometriosis. Now we know that the prevalence actually varies in different groups and in the tools that you use to make the diagnosis, right? Among asymptomatic women, just walking

around, no problem at all, upwards of 11% of women can be found to have it. In women who have subfertility, it can be somewhere between 21% and almost 50%. And among women who have chronic pelvic pain, it's at least three-quarters of those women have some element of endometriosis. Now I think what is new also in this burgeoning area of understanding is that the prevalence of young women is coming to be much greater appreciated. We always thought it was a disease of women in their 30s or a problem there, but we are finding teenagers have endometriosis and teenagers are symptomatic with it. Now it's kind of interesting that among the women who are unresponsive to medical therapy for pelvic pain upwards of three-quarters of those women have endometriosis. So it's all over wherever you look, and I know you're seeing it in your practice, so you're going to be as excited as we are with some of the progress that has been made.

As I said, the average age of diagnosis is in the late 20s, early 30s, but 52% of women are actually diagnosed between 18 and 29, right? If we're talking averages, it's 28. The sad number is, and I think please put this in big, bold writing, 86% of women were symptomatic for 7 or 8 years before their diagnosis is made. And what are the symptoms they're suffering from, right? You can see the numbers there. Dysmenorrhea, pelvic pian, and dyspareunia. We know that endometriosis has impacts way beyond just what we're seeing in those numbers. We know that they're almost 2.7 times more likely to have severe symptoms when they have other pain. So if she has interstitial cystitis and endometriosis, which is magnifying her suffering from interstitial cystitis, and it's not just that as a factoid, but because she has endometriosis, it's much more likely that she has other coexisting conditions that can be adding to her suffering.

We have sort of the broad-brush risk factors for endometriosis. Family history certainly plays a big role. We see a huge increase if a first-degree relative has been affected by endometriosis. Other things: frequent or heavy menses, early menarche, nulliparity – particularly when it's not chosen, right? When it is a reflection of an inability to conceive rather than a decision not to. Low BMI, alcohol use, autoimmune disease, we're seeing that linked in, too, and then we're finding those genetic variants that we talked about that are becoming much more common, and we're seeing the patterns in different families, different cohorts being all related not only to endometriosis, but as you can see there, associated conditions like uterine fibroids.

I just want to emphasize again the endometriosis among teens because, interestingly enough, the signs and symptoms actually do differ slightly from adults, that they're much more likely to have acyclic pain with or without cyclic pain, and oftentimes they complain primarily of GI symptoms rather than GU symptoms. Migraines are more prevalent among teens who have endometriosis versus other teens. And look at this, a third of teens said their dysmenorrhea and the pain that ultimately was diagnosed as being resulted from endometriosis actually started before age 15. So this is astonishing and it takes her until she is 28 on average to be diagnosed.

Well, the endometriosis impacts? The two big ones, you know, broad-brush stroke here, pain and infertility. And I think what's important here is the costs that are associated with endometriosis are similar in magnitude to cost for type 2 diabetes, Crohn's disease, rheumatoid arthritis, those are all big-ticket items, and so is endometriosis. We know that the cost of care to manage the whole spectrum of symptoms that occurs with endometriosis is much greater. It certainly affects the physical, mental, sexual, and social well-being, as well as women's productivity in the workplace, in the home, altogether. And the societal burden of endometriosis has really been estimated to be a staggering number that you see here before. We know that the pain is intense, that women with endometriosis are 3 times more likely to use opioids than controls are. And some estimates say that up to two-thirds of women with endometriosis, symptomatic endometriosis, do rely on opiates at some time or other for control of this type of pain.

So what are the endometriosis-related symptoms? Well, we've already talked about chronic pelvis pain, and that would be the acyclic constant pain that's there. Intense dysmenorrhea, deep thrust dyspareunia, even dysuria, right? When the bladder is locked down or inflamed, it's going to hurt to urinate and it's going to hurt to defecate. And just the pain itself can be exhausting, so she can have fatigue, infertility, we talked about, and certainly as we added the layering of the pain, somato-sensory amplification of other nociceptive inputs can certainly arise as a result of her chronic draining from her endometriosis. And I think you can see this all adds up to a significant decrease in the quality of life.

Why is it that we have such wide ranges of manifestations? Well, you know, a lot of it has to do with the maturity of the endometriosis and the location, all of those types of things and that – the organ systems that are involved. So when we're doing, say, laparoscopy, you can see very superficial peritoneal lesions. And they can be clear, which makes it very difficult to detect them; they can be yellow. Now some of them have read the textbooks, and they're supposed to look like powder burns, either blue-black or something like that. So, classically, there can be some of these and they have a little pinching to them, a little puckering of the tissue around, but they can be all over, any peritoneal surface. Then there can be localized within the ovarian tissue itself, where she's actually bled in below the capsule and there's old hemolyzed blood sitting there waiting to burst and have a chocolate cyst fluid all over her peritoneal cavity and have a surgical emergency. What's really challenging from a management standpoint, and particularly if we're approaching this with surgery, is the deep infiltrative endometriosis, and particularly when it's in the retro space there where there's high vascularization of the lesions and that encourages more enervation, which then amplifies the pain that's there. In addition to that, as a result of the perpetual monthly shedding and the inflammatory response to that shedding, we know classically scarring and adhesion formation can occur throughout

the pelvic cavity and affect the function of those organs, not only the fallopian tubes, but the bowel, right, we understand that. And there are lesions that appear outside the pelvis that can cause their own problems.

Now, classically, we've recognized that adenomyosis and uterine fibroids have been closely linked, we're beginning to get some of the genetic explanations for those. But what's really interesting now is that there is emerging evidence that both clear cell and endometrioid ovarian cancer may be associated with endometriosis. And several autoimmune diseases have been associated not only in a genetic level, but also in an epidemiologic association.

Well, again, pathophysiology, we certainly appreciated the insights of Samson in the classical 3 mechanisms of spread, the primary one being retrograde menstruation, but also recognizing that the whole of the peritoneal cavity with its coelomic cover was susceptible to metaplasia and could convert into endometriotic tissue. And then that not only did it go directly into the peritoneal cavity, but with retrograde, you could get it into the lymphatics and the vascular metastases that help explain why it is we find it on wrists and eyeballs and all kinds of really weird places like lungs. But today we recognize there's a much more complex process involved that is an interplay between immune factors, right? We always knew that there was an inflammatory responses, but why is it that some people get endometriotic tissue in their peritoneal cavities and it doesn't take root, right? And why do some people have a small amount of endometriosis not progress while others do? Clearly there, we've understood the hormonal factors in a very broad-brush way, but to divvy down into it and to understand a lot better those interactions. The fact that it's inflammatory disease is important, and as I mentioned, the heritable factors have really emerged in the literature as being new, very fertile areas to investigate.

So now we can look at endometriosis beyond just the individual patients, but really to really look at it as a public health problem can be important. And we can do this because it, as we said, it has a major impact on the quality of life of the affected women and on the economic costs. And we understand that now the diagnosis can be based a lot more on a structural process of the patient interview, the clinical examination, and maybe some imaging studies, that we need to really rethink our old approach of, we want to rule out endometriosis; she's got to have surgery to make the diagnosis. And really consider the patient's endometriosis life. We recognize that particularly medical management is the first-line therapeutic option for women who have pelvic pain and no desire for immediate pregnancies and don't have other pelvic pathology that would require surgical examination. And we know that modern endometriosis care really should be individualized and can be because we have new ways of approaching this. We want to use patient-centered, multimodal and interdisciplinary integrated approached when helping women learn about their endometriosis to help design their therapies, right? And to help set their expectations and understandings about this condition.

We know it's not easy to make the diagnosis. For number one, there's the patient's hesitancy to bring up the problem when she's got a new provider. Maybe because she's talked about it before and it didn't get anywhere, she was really disappointed, maybe she feels stigma from having this, and so the diagnosis maybe was missed or maybe treatment was incomplete. All of these types of things play into the women's willingness to really share with us what is her past experience and voyage with its disease process. The other thing we've already mentioned is the variety of physical manifestations, right? And the impacts they have on the symptomatology itself. And I think, clearly, that the symptoms can be very nonspecific. Some women could be asymptomatic, or it can come to be crippling pain, so that wide range. Sometimes the same intensity of endometriosis, if you will, but it manifests itself so differently. And the fact that in the past we've relied on surgical procedures to make the diagnosis presumptive clinical diagnosis was really discouraged. And I totally understand that in clinical trials we really do need to have biopsy-proven disease and we move on through that. But in practice today, we do not have to have that huge hoop that she has to overcome: finding the time, finding the money, finding the clinician to do it, all of those types of things. And honestly, there really is a lack of public and, I have to confess, professional awareness of the magnitude of this problem and the diversity of its presentation.

And it's not an easy thing, patient comes in with pelvic pain, what's on your list of differential when she comes in with those types of things? And these are just level A things; this doesn't have B, C, or D, all the other thing that it could be. You know, adenomyosis, interstitial cystitis, it can be – mimic the gyn or GU or GI malignancies right? Dysfunction of the bowel function itself with IBD or IBS, celiac disease, and then pelvic adhesions from other sources, either old PID [pelvic inflammatory disease] or surgical infection can make it. And then we have all the other pain syndromes, we have fibromyalgia and myofascial syndromes. You can just add the little, all the things that really focus in the pelvis, and we can have neurological disorders that can do this. And of course the overlay of depression and anxiety can certainly play important roles in women who have pelvic pain and might be considered to have endometriosis.

So as we're considering what kinds of strategies we want to have for patient care, I think we want to think about what are we going to do about her acute symptoms and the problems, what she's dealing with right now and how it's impacting our quality of life and her relationships. We have to consider seriously that she's at high risk for having comorbidities that may be playing into this. And then we want to know from her, what are her reproductive life plans at this moment? We also have to consider not only what's going on right

now but what are the longer-term health consequences if we don't intervene? Very importantly we need to get her input. We want to find out what her preferences are, not only for therapy but her input and her understanding of what's going on with her and how she's interpreting these processes and what it means to her so that we can really communicate very effectively. And I think we need to work with the patient to let her help set her expectations for whatever we're doing, that there isn't any magic wand today that can cure endometriosis now and in the future.

What else do we have as a challenge? Well, women are certainly relying a lot more on social media to get their information. Particularly as their resource for people who have complex and debilitating health conditions, and that's certainly what fits endometriosis to a T. And we know that our patients, right, turn – clearly, reproductive health-related concerns make up the vast majority. Look at that, 90% of social media health inquiries made by women have to do with their reproductive health. And women in pain are twice as likely to use social media to understand and to manage their GYN conditions. So we have a partner, a silent partner; we don't even know what she's being told, right? So we need to find out what she's hearing elsewhere so that we can help her understand that or disbelieve it or whatever else. And patients with pain are almost twice as likely to trust the information that they find on the social media. Sometimes when we don't give them as much hope, then they will turn to other things that promise even better results than we can offer.

So what are the current approaches? Endometriosis is now clearly recognized as the clinical diagnosis initially. We need to do a complete pelvis examination. Surgery is still very important, but it can be reserved for cases that don't respond to medical therapy, cases with pelvic masses, or she has an acute presentation, a ruptured endometrioma, right? And there certainly is lots of room for individualized indications, and one of those big ones is desire for fertility right now. We want to design therapies that address women's current complaints but also will bridge to the long-term suppression to reduce the risk of recurrence. So the perfect little surgery that eradicated all the implants is a great accomplishment, but now what are you going to do to keep it from coming back? So we want to always blend these things, either complete reliance on medical therapy or some pairing with surgical intervention, but always in a mind that we have to be alert to try to reduce her risk for recurrence.

The imaging studies can be kind of limited. You can't see a tiny little implant. You can see larger nodularity, you can see constrictions, you can see endometrioma, right? A transvaginal ultrasound is really quite sensitive and specific for that. You can add color Doppler flow to see a little bit more what's going on with the little mass that you're seeing. Maybe 3D imaging holds a little bit more promise for us, just as it did when adenomyosis. Transrectal ultrasound certainly helps us look at the infiltrates in the bowel wall. We can see other issues that are there. And certainly, the emerging role of MRI can be very important.

Unfortunately, lab testing is not going to be very helpful. CA 125 is usually elevated and sometimes I've seen it be, you know, in the thousands with endometriosis, but it's so nonspecific it's really unhelpful. And while there are some biomarkers, there's obviously vigorous energy being developed to come up with a blood test to say whether or not she had endometriosis. But I bet you can already imagine that things like menstruation and some of those other things might cross-react and make it more difficult to develop a clear biomarker that will say this is endometriosis.

I think we want to move on now to some medical therapies. And classically, we've approached the medical treatment of endometriosis with one or the other hormonal effects. One is the pseudodecidualization and the atrophy of the implants or creating a pseudopregnancy. And that's what we usually get when we use progestin-only therapies or progestin-dominant combined hormonal therapies like birth control pills. Another approach has been to create a pseudo-menopausal state so that we suppress the estrogen stimulation. So on one hand, we're counting on the progesterone to downregulate the estrogen receptors. In the other approach, we cut off the estrogen entirely or its effect on the endometrium. And we did that with GnRH agonist aromatase inhibitors or the old danazol, the androgens was to block the activity on the estrogen receptors. Now this is usually – while we're dealing with these hormonal approaches, we always want to combine it with inhibition of inflammation and for treatment of pain. And that's where the role for the NSAIDs and the opioids come in. And again, just to stress that the important point is that all of these things are treatments; they are not cures.

What has been first-line therapy? Our combined oral contraceptives and, these days, vaginal rings, hormonal contraceptives have kind of joined in that same first line, first tier, because it's the progestational effects that are the key to success. And we find that two-thirds of women actually do have relief from pain and have marked improvement in quality of life when you use these – there's a reason they're the number one choice, right? And just some tips, it's so much kinder to use continuous use rather than making her bleed every month, particularly when she suffers from dysmenorrhea. Making her dysmenorrhea less rather than none is hard to defend. And what we've seen with continuous use of these combined hormonal contraception following surgery, there's less recurrence of dysmenorrhea or nonspecific pelvic pain, and the development of endometrioma are less if you give particularly the continuous therapies. But we have to be humble. We know that progestin resistance can develop. You may get an initial response, but two or three years later, it just doesn't seem to be working as well, and she's coming back asking for new ideas. And if we look at the bulk of the literature, the Cochrane Analysis really says that there's insufficient evidence that treatment with COCs is superior to placebo, and the reason for that is that they

find that many of the studies have high degrees of bias in them. But we still – and it's still listed in all the guidelines that COCs and combined hormonal contraceptives are first line. And we have studies that desogestrel multiphasic pills are as effective as GnRH analogs in some published studies. But I mentioned already that even if we have initial success, which we can certainly celebrate, that upwards of a quarter to a third of the women may initially have or develop progestin resistance.

Couple of things for progestin-only therapies. Progestin-only pills may be better than combined therapies if we get – maybe then we can be studying that in a new, stronger progestin-only pill. And where we have data, in particularly dienogest, which is a specific progestin that we don't have as a progestin-only here in this country, but because it has anti-angiogenic properties, it can actually shrink implants and reduce pains. And of course, what you've been working with, using the LNG-IUS when we can. And then the LNG – the etonogestrel implant, we can see reductions in pain scores – substantial decreases. And of course, the implant has the benefit of suppressing ovulation so that it – and perhaps more affecting estrogen production by the ovary. Following surgery for endometriosis, LNG-IUS has been shown to be effective in pain suppression, and I think people forget that it actually has been shown to be as effective as the injectable GnRH analogs.

Continuous DMPA reduces pain more, even more so than continuous oral contraceptives. And a really dirt cheap way of approaching this, and people don't know this – not dirt, dirt cheap – but certainly subQ Depo Provera went head-to-head with GnRH agonists and found to have equivalent symptom relief. And so that subQ Depo actually carries FDA approval indication for the treatment of pain syndromes with endometriosis.

So we've certainly looked at a wide range of, of hormonal therapies and you know that we've used GnRH agonists such as Lupron and goserelin, we've used androgenic steroids and emerging options, the ones that we're very excited about, are the new introduction of the GnRH antagonists. Off-label use of aromatase inhibitors has shown some promise, and selective progesterone receptor modulators, so-called SPRMs have been tested in Europe, but not in the United States. We only use that compound for emergency contraception.

So what is new? And I do want to highlight here this whole new class of GnRH antagonists – not agonists, but antagonists that work specifically to block the impact of GnRH on the pituitary. So it's an antagonist, sits on the receptor and shuts down any communications between the hypothalamus and the pituitary. Very effective, very rapid onset.

And the FDA approved elagolix as the first oral GnRH antagonist and it was specifically developed for the treatment of moderate to severe pain associated with endometriosis. And it has very strong clinical data from 2 similar double-blinded studies. They called them, if I can, EM1 and EM2. And let's just quickly look at them. Both of them were randomized 6-month studies, phase 3 studies, and what they looked at was low dose, 150 mg once a day versus a high dose of 200 mg twice a day. And we can see that they got 800 women randomized into those 2 arms, and what they were looking for was clinical response to women who came in with dysmenorrhea and with nonmenstrual pelvic pain and they looked at it at 3 months, and they also assessed the outcomes at 6 months. And I think you can see here, clearly, in the green we're looking here at results from the studies and we're looking at what was the difference, right? How much of a decrease did they experience in their symptoms, in the dysmenorrhea and the nonmenstrual pelvic pain in the first study and the second study. And the green is the placebo. And we can see that in dysmenorrhea, about 20% of reduction in the pain associated compared to baseline. The low-dose version once a day is in purple there, and we see about a 50% reduction, but the twice-a-day dosing at the high dose really reduced pain by about 75% at 3 months. And we can see that those numbers were sustained through when therapy was continued through 6 months. Nonmenstrual pelvic pain, there the difference between the doses was not quite as remarkable, but nor was there a huge difference between that and the placebo. Now let's look at the second series of studies, and you can see if we just line them up the way they are, that there's great similarity. And it's always wonderful to have that kind of separate study going on, right? So that you come up with results that are very similar; it really adds believability, right? And you can see the comparability of the study's results in each of the dimensions both for the placebo and for each of the doses that were there. So they extended this study. They evaluated the efficacy and the safety of elagolix for over 12 months and that meant that an additional 6-month treatment was given to women who had been in the phase 3 studies, and they continued the same 2 dosing studies. And what they were looking at again there was clinically meaningful pain reduction and nonmenstrual pelvic pain scores. And they also, in this one, looked at data on dyspareunia. And I'm not going to go into all these numbers, I promise you. But we can see that dysmenorrhea was reduced in both. So there was a continuing improvement in the percentage of responders in the lower dose, and it pretty much stayed the same with the higher dose in both of the arms. And nonmenstrual pelvic pain, continued use actually continued to improve the situation for nonmenstrual pelvic pain in the low dose, and dyspareunia also tended to improve in the lower dose, but the gains that have been made in the higher dose. So women kind of got to a higher place and held it with a higher dose, whereas the women who had the lower dose continued to improve, and that was true in both of the studies that they had.

So the quality of life was assessed in this study in a 30-item endometriosis health profile score, and it looked at several core domains, the pain, the control, and powerlessness, emotional well-being, social support, and self-image. And they also added 5 questions on

intercourse, which I think is really important. And we can see that the elagolix therapy over the 6-month period significantly reduced those pain scores, all right? So we had improvement across all the domains. And once again, the higher dose twice a day was more effective than the single dose, lower dose once a day.

Well, there's another player that is coming into the field and that's relugolix. It is another oral GnRH antagonist, and its data is currently under review at the FDA for treatment of moderate to severe pain associated with endometriosis. And their clinical trials are SPIRIT 1 and SPIRIT 2 and they're doing the extension studies similar to the design that we saw here. And it's expected that the FDA will respond sometime in May. But we got a little bit of a peek, we don't have a lot of published data as we had for the early well-established product that was there. But we can see just at ASRM that when they compared baseline scores from to women who are randomized into relugolix versus the placebo, and here we're dealing in each arm with about 400 women, that the pain scores dropped much – statistically significant, 0.0001 was the *P* value, but the difference is between the change in baseline scores for the total scores. And where you saw in every single category pain, emotional well-being, again, control and powerlessness, the self-image, and the social support, in general, the improvements in each of those categories was at least double in the treatment compared to what we saw with the placebo. So I think those are going to be important to us as we move forward and we look forward to having the peer-reviewed data.

There's a third agent linzagolix, and this is currently in clinical trials. It's another GnRH antagonist being studied for the management of endometriosis, and it has 2 – there was a phase 2b study that has been completed. And that was the dosing study that looked at 3 different doses for 24 weeks and allowed an extension for 52, and the primary endpoint was the proportion of women who had at least a 30% reduction in pelvic pain over a full 28-day cycle. So that included the dysmenorrhea as well as the chronic pelvic pain. And at week 12, significant reductions were observed at the at the 75-mg dose or more, and it actually maintained – that kind of relief was maintained through 52 weeks.

So what's happened? Have we completed those phase 2b studies? They're moving on now to pivotal phase 3 clinical trials, and again, they're hoping to get this done later this year. And we'll see data on approximately 450 patients and, again, looking at the endpoints where they're endometriosis looking at the GnRH antagonists itself without add-back therapy as well as with the add-back therapy.

What other medical therapies are currently under investigation? Well, we mentioned the aromatase inhibitors shut off estrogen production altogether. We mentioned the selective progesterone receptor modulators, if we were to get UPA in this country. But where are we moving in the future? Away from just playing with the hormones is to look at immunomodulators. Can we turn off the immune system that plays such an important role in the inflammatory responses to the endometriosis itself? As we saw with dienogest, can we inhibit the ingrowth of blood vessels to these new endometriotic places so that they can't grow, to sort of starve them if we can? Can we target the matrix metalloproteinases, again, that are so key to that inflammatory response that we see? And it cleaves the area off and creates these dead necrotic cells that become the target for the inflammatory cells. Can we directly work with estrogen receptors and inhibit them rather than working with blocking the production of estrogen itself? And then are there other GnRH antagonists that we can talk about in the future?

So having gone through this story, I think we can all appreciate there's just been progress in so many different dimensions over endometriosis. There is a new appreciation that this is a chronic, progressive, inflammatory process that has systemic health impacts, that we have a new understanding that adolescents and young women are frequently affected. And we see that there is a sadness in that there is this delay of at least 7 years. Even though we have been looking for it, we need to be even more diligent in our search. And new practice approaches for diagnosing the condition really minimize the role or the necessity for surgery. And we have new medical therapies to treat and suppress the condition itself. So this is such a patient-centered problem. I mean, she is the one who's suffering the issue here. So really need to circle back and looked at shared decision-making where both the clinicians and the patients communicate using the best available information when making decisions. And that there are steps. We introduce choice. We describe options. We help patients explore their own preferences and help make collaborative decisions. And that helps us understand the risks that area associated with the condition. We're not just focusing on the risk of the procedure or the treatment, but really put it in the background of the risks that she faces from having endometriosis. Help her understand what her options are, the risks, the benefits, alternatives, and the uncertainties. And weighing – helping her weigh her own personal values regarding the potential benefits and harms, and finding out what matters most to her in this equation so that we can really respect her values. And participating in the decision-making at the desired level.

Now what can we do for endometriosis? And you can see here we have some tools. In general, we want to listen attentively to the patient, what her goals, her fears, and her previous experience have been. Develop a relationship of trust and teamwork, we do this all the time, right, but really putting it in the context of endometriosis, I think, is a wonderful activity. Use decision aids whenever we can. Let her visualize what her options are and be able to kind of integrate them and see the pluses and minuses. And for the treatment benefits and risks, talk to her about what the goals of the therapy is, again, this isn't a cure, is it? It's a treatment. We're trying to work

with the problem that she has and minimize its impact on her and promote her health and well-being. Personalize the treatment selection, and so the management plans really need to consider how much – how severe her symptoms are, what her potential is for recurrence if we irradicate it now, what her desires for fertility are, and so many of the other things that affect a woman's decision in anything: how much cost, what are the side effects, how does it – the route of administration, how is this feasible for her to do, right? And then talk about what she fears the risks might be, either from the condition or the intervention altogether. And then we want to monitor her carefully once we've initiated therapy. Is it still working for her? Is she able to use it? Her compliance with it and how well is it tolerated? And, oh, things change over time, so we need to be nimble and have backup plans available.

So physicians, unfortunately, have very brief times to work with patients, and after we gather and listen as thoroughly as we can, discussing with the patient the treatments oftentimes can be quite abbreviated. And an office visit of 7.5 minutes just doesn't leave you very much time. Surveys have shown us that informed decision-making occurs in the minority of the office visits, and actually physicians ask patients if they have questions in less than half the office visits. So how is she supposed to be a real partner in her therapy if she doesn't even necessarily understand what we're telling her or she hasn't had a chance to clarify what it is. And perhaps as a result of all this rush and the lopsided communications, patients really recall only a fraction of the information that we present. So it's up to us to make sure she does understand, and we may have to make it into bite-size pieces. We may not be able to go to A to Z within endometriosis within 7.5 minutes; I haven't been able to do so.

So there are lots of potential benefits from effective risk communications and shared decision-making and certainly the improved adherence with therapy and improved health outcomes and quality of life. All of these are just so valuable, that the investment in making sure that she is a partner in her own care really play out in the long run.

So coming back to what we started with, that we really do need a team approach that involves the patient, primary care, the person whose – if the primary care is not taking care of her reproductive health, then the OB/GYN, and we can see the whole area. And of course, very important in all this equation is the insurer and what resources and social support the patient has, the family's understanding of what's going on. So pulling together this team to help the woman maximize the benefit she can get from the therapies we have to offer really can pay off in the long run.

So thank you so much for your attention and I look forward to your questions.

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