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EndoShare: Patient-Centered Management of Endometriosis

Dr. Singer:
So let's first start, we have all heard about endometriosis, but what really is it, and let's perhaps start with the definition and talk about what people need to know.

Dr. Cohen:
So dysmenorrhea, painful menstrual periods, are the main problem. One of the problems with that, is a lot of young women especially, think painful periods are their lot in life, they don't think they have a disease, they think that's the way the world is, that's what happens. So dysmenorrhea number one, still remains the most common cause, I mean the most common pain, but not the only pain. Non-menstrual pelvic pain, I like the words, we used to call it chronic pelvic pain, but now we call it non-menstrual pelvic pain, is the second more common pain and dyspareunia, first of all, not everybody is having intercourse, so dyspareunia is the third most common pain and then there is all sorts of pain that you can see on that slide as well.

If you don't see endometriosis in your practice knowing that one of ten women have endometriosis pain, then your eyes are closed, okay…If you think that everybody with a painful period doesn't have endometriosis is just her uterus contracting, then you are obviously missing the diagnosis. So, yes, the answer to that is yes, they are missing the diagnosis.

Some of it is patient related, they don't bring it up, they don't come in, the pain is not as severe that it needs treatment, they don't want treatment. There is a number of reasons that the delay may come from the patient and this is sheer decision making, from the patient's standpoint. There is delay from the provider. Again, if you don't see endometriosis in your practice, you are going to have a delay in diagnosing.

Dr. Singer:
You describe some gastrointestinal symptoms and genitourinary symptoms that can go along with endometriosis. Sometimes they may be the presenting symptoms, but what else do we need to think about in the differential diagnosis, in other words, are there other primary problems that could really be what is going on as opposed to endometriosis?

Dr. Cohen:
It is one of those decisions that you need to rule out the other things the best you can, and that is not easy, to make sure you are treating someone or you are telling them that they probably have endometriosis and they probably do. So, there is a list of the things that basically can mimic the pain of endometriosis. Again, it can be chronic or cyclic and it can be IBS or inflammatory bowel disease, chronic constipation, cancer – we have seen a few over the years, but not usually, doesn't mimic, and the urological disease I think mimic even more, chronic UTIs, but particularly the number one thing on that slide is IC, interstitial cystitis. It mimics exactly endometriosis pain.

Dr. Singer:
So the first is, what are the appropriate questions to ask the patient to try to get to the diagnosis? Okay, that will be easy. The second is how do we make the diagnosis and then I want you to talk about whether or not imaging is helpful and whether laparoscopy is

necessary.

Dr. Cohen:
When you have a patient with pain, you ask basically the same initial questions, what makes it worse, what makes it better, when does it start, when does it go away? All those types of things and then you are going to put on your general practice hat and ask the questions about the other diseases, trying to "rule them in or rule them out."

I know in this day and age, imaging is what everybody does. If you walk into, if you come into the ER before a history or physical is taken, you have imaging done, you know. And then you say "What was the problem" and they say, "Oh, I don't know, we didn't know she was over getting a CAT scan."

So you know, I think imaging is the way that everybody does things, but I think… You can be a visitor in Syracuse at the hospital and you'd end up getting a CAT scan.

Now, you know, but I think in this disease it doesn't really help you and it also doesn't help you in that list of other diseases that was on that slide that caused pain, because the resolution of endometriosis, no one is going to see endometriosis on any imaging or any of those other diseases, IBS (inflammatory bowel disease), probably not. Now I am not talking about stage 3 or 4, but you can make that diagnosis doing a pelvic exam, when the pelvis is fixed it hurts. You can make that diagnosis, ovarian endometrioma. I'm not saying don't get an ultrasound to maybe help you make sure there is not some sort of big ovarian cyst or something going on that you didn't feel, but to do advanced imaging, I don't think is helpful at all in this disease.

Now we are talking about laparoscopy and endometriosis comes in two different ways. One is for diagnostic testing, the other is for treatment. I'm not saying we don't do laparoscopy for treatment in recalcitrant patients, but we don't need to do it for diagnosis. We can make that diagnosis clinically and the drugs are proved to be used empirically.

Dr. Singer:
Once the treatment is established, what are the treatment approaches? Surgery? Medical treatment? Or both?

Dr. Cohen:
Endometriosis treatment is a medical disease. Endometriosis is best viewed primarily as a medical disease with surgical backup and I think that is the best way to think of this disease.

Dr. Singer:
So both ASRM and ACOG sort of talk about endometriosis as a medical disease with surgical backup. Let's talk about some of the medication categories or types of meds that are available for treatment and I would like you to concentrate on the first four categories on this slide because then we are going to talk more in depth about the last two.

Dr. Cohen:
So this is a neglected disease. If you look at that is list you think "Ah, nonsteroidals, you can buy those over the counter, that's the least effective treatment," but it is the most specific treatment we have because everything else we have on that list lowers estrogen. That's how it works. It lowers estrogen. If we lower estrogen, the endometriosis that is dependent on estrogen, gets less.

What about oral contraceptives? Why are we giving combined oral contraceptives, and every society recommends it for pain of endometriosis, that have more biological estrogen in it than anybody's physiological estrogen. So we know that endometriosis is dependent on estrogen, why are we giving them estrogen? Does that make any sense? In reality, it doesn't make any sense and in fact, what are we doing? If we are going to use oral contraceptives, how about progesterone only? There is no reason to give the estrogen in that pill to someone who you think has endometriosis. It would be counterintuitive. Now when we look at the rest of the list and I am only going to talk about the next two on this slide, everything that lowers estrogen, and all of those next four things do, reduces bone density. So that becomes the limiting step and the side effects of hot flushes. That is really what we are dealing with. Progestins no matter if it is Depo-Provera or an IUD, maybe not so much, Danazol doesn't really lower estrogen as much, but Danazol is an androgen, okay, it is a modified androgen and it was very successful, it does lower estrogen, it was very successful. We used it for a while back in the 80's, 70's, but the patients had less pain, but they all looked like the Smith brothers on the cough drop box, okay.

Dr. Singer:
Okay so with that, let's move on and let's talk about GnRH agonist therapy, because this has really been the mainstay of therapy for a number of years.

Dr. Cohen:
Okay, so GnRH is one of the drugs that is approved for endometriosis therapy. It's an agonist. If someone said do you want an agonist that is going to stimulate the pituitary and increase estrogen in the beginning or do you want an antagonist that is going to block it, you

would say give me the antagonist, I don't want an agonist, and yet, we used it in the beginning because we couldn't come up with a drug that could be given usefully and the trouble with GnRH is what you see in red, is the hot flushes and night sweats. So that was one and the second major side effect, which the patient's obviously had no symptoms of, was losing their bone density. So it was the hot flushes that made patients stop and the bone densities lowering that made the FDA tell us, we had to stop the drug after a certain amount of time. It was injectable.

Dr. Singer:
It is always refreshing to see new advancements in the field, so let's talk about the new kid on the block, elagolix, and how it's used in terms of managing this important condition and ways in which it may be different or similar to GnRH agonist therapy.

Dr. Cohen:
So this is the first drug in about 20 years, okay, and what it is as you can see in red, it's an antagonist. Now we have been using antagonists for almost a decade in GYN, we used it by injection on a daily basis to prevent IVF patients from ovulating their eggs and splitting them out all over their abdomen before we can retrieve them. But it wouldn't have been practical, daily injections of an antagonist, so they were able to make it in an oral form and it is approved by the FDA for moderate to severe pain.

Dr. Singer:
So talk a little bit about the way it works

Dr. Cohen:
So it's pretty straightforward how this all works and on the right side of the slide, you can see the telephone poles of the receptors and the triangles of the GnRH and the magenta balls, actually is the antagonist blocking the receptor. It is very quickly reversible, comes right off that receptor, but it is very quickly effective as well.

Dr. Singer:
Look at the video to sort of show this.

Narrator:
The hypothalamus produces endogenous GnRH that binds and stimulates its receptors in the anterior pituitary, which leads to the release of LH and FSH. LH and FSH stimulate ovaries to produce and release estradiol and progesterone, driving the growth of normal and ectopic endometrial tissue. Drugs known as GnRH agonists super-stimulate pituitary receptors to produce large amounts of LH and FSH. These large amounts of LH and FSH lead to high levels of estradiol and progesterone that temporarily worsen endometriosis symptoms. This is known as the flare response. Eventually, GnRH agonist stimulation fatigues the pituitary, resulting in decreased release of estradiol and progesterone from the ovaries. By contrast, drugs known as GnRH antagonists have a more immediate impact on reducing the levels of estradiol and progesterone released by the ovaries. Their MOA is to reversibly bind with endogenous GnRH receptors in the anterior pituitary. Decreased pituitary stimulation lessens the release of LH and FSH and subsequently decreases estradiol and progesterone release by the ovaries. Thus, the use of GnRH antagonists quickly reduces estradiol and progesterone levels.

Dr. Cohen:
And just a word about how this is different than the agonist. The agonist down-regulates. It is not dose related and it down-regulates the pituitary, so basically drains it of production. This does not down-regulate, it is a competitive inhibitor. It sits there and blocks the drug, so they are very different drugs, although they have a similar effect in lowering the estrogen. Look how fast this drug works. This is low dose and high dose, not important right at this time to talk about, but you can see that in 24 hours after you take your first pill, look what happens to you estrogen level – it plummets down, but not so low that you get those severe hot flushes. There is a window; it is dose related, so it happens very quickly with one pill. Its peak serum level is an hour, so its T-max is an hour, half-life is 6 hours and it comes down very quickly and it is reversible. So look at the dysmenorrhea scores. I can show you a lot of scores we did during these studies to get them approved by the FDA. If you look at the top left hand column, that is when patients walk into the office, their pain score is 2.2 on a 3 point scale, they have moderate pain and they have no change in their pain because they haven't started the drug yet. And look how fast this drug affects their pain. If you look at month one, down at the bottom, you can see that their pain is gone even on low dose, has almost dropped a whole point out of 2.2, so it's down in the mild range and if you are on the high dose, it has dropped a full pint in one month and in two months, look how far you have dropped. You have dropped 1.7 out of 2.2 on the high dose and a good 1 on the low dose form and so you've got very good affect and you don't have to wait months and months to find out if it is going to be effective. Maybe you're wrong in your diagnosis and the patient doesn't have endometriosis. Maybe she just has a lot of adhesions and she is not going to get better. You will know in two months whether you are going to get a good affect with this drug, so it is very helpful in that regard; it is very quick. It is oral, but it is very quick.

Dr. Singer:

So it is exciting that we have something new. This next slide is really just to remind us that there are other therapies under investigation, so sort of stay tuned, some of them hopefully will get more at the mechanism of disease.

So in the last moments, I want to focus on how we can work together with our endometriosis patients and really this concept of shared decision making and patient-centered care. Do you have any pearls for discussing fertility and quality of life with patients, other aspects in terms how we might choose the right treatment for the right patient?

Dr. Cohen:
Yea, and I think its communication and just talking to the patient and finding out what she wants. Endometriosis is a disease that affects, it's not like having elbow pain, okay, or knee pain. It affects your whole family, everybody around you.

Dr. Singer:
And that I guess is really the key, right? It is listening to the patient and then talking about having an open dialogue so that we know what the patient's goals are, what's important to them and we can potentially match treatment approaches based on what's most important to them.

So there is a website endoshare.com that you see at the bottom of the slide and that is really somewhere that patients can go to report symptoms. Much of what we do today focuses on patient input, patient reported outcomes. The more data that we can gather, we can figure out what is best for patients, so that is certainly a site that you can suggest your patients visit. There is a lot of educational information that is also available.