New Aspects on Diagnosis and Treatment of Endometriosis

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Dr. Hugo Verhoeven: "Hello, my name is Hugo C. Verhoeven. I am a member of the Editorial Advisory Board at OBGYN.net, and I'm reporting from the 3rd International Meeting of the European Fertility Associates in Zurs, Austria. This afternoon I have the honour of interviewing Professor Ivo Brosens, who is a consultant at the Leuven Institute for Fertility and Embryology. Ivo Brosens is certainly one of the leading experts in the field of endometriosis. Professor Brosens, good afternoon, and thank you for giving me the pleasure of interviewing you. In the last few years, not that much has changed in the diagnosis of endometriosis. Now, you've found some new concepts, and those concepts are not only important for the diagnosis of endometriosis, but also for the treatment of endometriosis. Please tell us about these new concepts concerning the diagnosis and treatment of endometriosis."

Professor Brosens: "Thank you very much, Dr. Verhoeven. We have seen in the field of endometriosis, particularly during the last ten years, some very important publications that have changed today's concept of endometriosis. Sampson proposed the concept of dissemination of menstrual blood into the pelvis and implantation, as published in 1927. Since that time, the whole community working on endometriosis has tried to prove that this theory is correct - that menstrual cells are alive, pass through the fallopian tube, adhere to the peritoneum, implant, and develop. Consequently, the diagnosis of the disease is based on the visualization of the implants. Before Sampson, the disease was described as adenomyosis. The disease was characterized not by bleeding implants, but by fibromuscular nodules, more as a solid tumour. Today there are three phenotypes of endometriosis: peritoneal endometriosis, ovarian endometriosis, and rectovaginal adenomyosis. So this was a first change in the appearance of the disease."

Dr. Hugo Verhoeven: "Maybe we should go a little bit deeper into the concept of these three different types of endometriosis. Could you comment on what exactly rectovaginal adenomyosis, ovarian endometriosis and peritoneal endometriosis are?"

Professor Brosens: "Sure. We are getting to the very important observation that endometriosis is a phenotype determined by the localization, or where it reflects the activity of endometrial-like tissue at that site. Now we talk about function in a way that is similar to endometrium. Superficial endometrium is characterized by cyclic bleeding. Cyclic bleeding in peritoneal endometriosis leads to inflammatory reaction and fibrosis, and in the case of ovarian endometriosis it leads to adhesions and endometrioma formation. On the other hand, with rectovaginal endometriosis the fibromuscular proliferation reflects the activity that we see at the endometrial-myometrial junction. Rectovaginal endometriosis has the morphological aspects of adenomyosis. Therefore, today we can classify the phenotypes into two groups, one which is characterized by cyclic haemorrhage and the other predominantly by the smooth muscle metaplasia."

Dr. Hugo Verhoeven: "Do these different types of endometriosis have different pain patterns? Does a patient with peritoneal endometriosis have the same pain as a patient with ovarian endometriosis, or rectovaginal endometriosis? I know that with laparoscopy you can easily see peritoneal endometriosis and ovarian endometriosis, but this is not the case with rectovaginal endometriosis. What is the difference in the way you diagnose those different types?"
"You ask very good, fundamental questions. Pain is a very difficult problem because we know there are patients who have a lot of endometriosis and no pain, and there are patients who have very little endometriosis and a lot of pain. The classification system of the American Society for Reproductive Medicine is all right for infertility, but not for pain because that isn't the stage which reflects the pain. It may be more important to evaluate the lesions in terms of function or dysfunction rather than by the presence and extension of lesions. For example, dysfunctional pain, like dysmenorrhea, is related to subtle lesions. At laparoscopy, we see the presence of small, early lesions with bleeding on the peritoneum in young girls who have dysmenorrhea. The dysfunctional pain is more related to red peritoneal lesions. On the other hand, dyspareunia and chronic pelvic pain appear to be more related to adenomyotic lesions, such as rectovaginal endometriosis."

Dr. Hugo Verhoeven: "So dysmenorrhea means painful menses, or painful menstrual bleeding, and dyspareunia is pain during intercourse? Until now, we were classifying endometriosis from the morphological, or visual, view. But now you are changing to another way of classifying endometriosis. What is that new point of view?"

"Endometriosis represents a disease in which the whole reproductive tract, or Mullerian canal, is involved. First of all, in patients with endometriosis, the peritoneal cavity is characterized by an inflammatory condition. Using techniques of underwater inspection by transvaginal hydrolaparoscopy, we now see that more than 50% of patients with mild endometriosis already have ovarian adhesions. It reflects the inflammatory condition. Secondly, the uterus is not responding to the sex steroid hormones in a normal way during the menstrual cycle. The endomyometrium responds in an abnormal way in the endometrium, and also in the junctional zone."

Dr. Hugo Verhoeven: "What is the junctional zone? This is something new, to me."

"The junctional zone is the third zone in the uterus between the myometrium and the endometrium, where smooth muscle cells are differentiated from mesenchymal cells. This zone is also hormone-responsive, and it is controlled by sex steroid hormones."

Dr. Hugo Verhoeven: "So between the inner layer, or mucosa, of the uterus, and the myometrium, or the muscular layer, there is an additional zone that we didn't know about until now. We couldn't see it on a normal ultrasound until now. Why did it take so long before we could see that third zone, the junctional zone? Why is that, and with what techniques can you see it?"

"The imaging technique with which it really showed up clearly was the MRI scan. The MRI shows a difference in structure between the junctional zone and the outer myometrium. Secondly, sonography has shown that there are contraction waves that are controlled by sex steroid hormones. Both MRI and sonography show that patients who have endometriosis have abnormal structures and functions of the junctional zone. In addition, the endometrium is also abnormal, but this is not seen on routine histology, so we didn't notice it. Biochemically, patients with endometriosis have abnormal endometria. In contrast with patients without endometriosis, the endometria in patients with endometriosis express aromatase activity. That opens the possibility to diagnose the disease without laparoscopy."

Dr. Hugo Verhoeven: "Let's make it a little bit simpler. What is the initial disease? Is the first step a morphological alteration, which means that those patients have another kind of junctional, or is the hormonal change first? What will provoke alterations of the junctional zone?"

"This is the question of the chicken and the egg. I certainly cannot give you the answer on what comes first. But today, what's more and more clear as we get into molecular biology is the local modulation of the response of the hormones by immune factors. Chronic inflammation apparently makes the microenvironment different from what is normal. Therefore, the steroids are not having the same effect as they would normally. We actually know that we have to look more and more for a
molecular definition of endometriosis. I'm not a molecular biologist, but I know that at the moment there are experiments in mice, for example, where they have knocked out the progesterone receptor and their development during the reproductive period is abnormal. The mice develop a syndrome that is similar to the human disease of endometriosis and adenomyosis. So it brings us to the situation where, in fact, endometriosis and adenomyosis are not different diseases, but are different phenotypes of an abnormal response of the tissues to the sex steroid hormones."

**Dr. Hugo Verhoeven:** "Now I would like to go back to the aromatase problem. What does this mean? Does this mean that, by performing an endometrial biopsy, you have a technique for predicting whether a patient is at a higher risk for developing endometriosis, later on? Or is the fact that you find a aromatase activity in the endometrium an indication that the patient already suffers from endometriosis?"

**Professor Brosens:** "Exactly. The expression of aromatase activity indicates whether a patient is very likely to have endometriosis or adenomyosis. At the moment, this has been shown in a retrospective study by a Japanese group and requires further confirmation by prospective studies."

**Dr. Hugo Verhoeven:** "Diagnosis is important, but what interests us even more are new concepts in therapy. Do we have any new ideas or hopes to offer endometriosis patients?"

**Professor Brosens:** “This very important question relates to medical therapy as well as surgery. Medical therapy for endometriosis started by giving patients estrogen, and they felt better as soon as the menstruation was suppressed. Later, pseudo-pregnancy therapy suppressed menstruation by administering high doses of estrogen-progesterone. Then we had Danazol, now GnRH agonists. The response to pain with these treatments is always very quick. As soon as the patient stops menstruating, she feels much better. But none of these medications is eliminating endometriosis. You can take any type of treatment for twenty years, stop treatment, and unless you are in menopause, you are very likely to have reactivation of the disease."

**Dr. Hugo Verhoeven:** "So this is a just a treatment of symptoms, not a treatment of the cause of the disease? It's not a cure?"

**Professor Brosens:** "Right. We are suppressing bleeding, which is causing the pain. Now, rectovaginal adenomyosis is a different story because we are dealing with lesions characterized by smooth muscle differentiation and proliferation. Adenomyosis also shows a sex steroid hormone response, but in a different way than endometriosis. It takes more time. If you give GnRH agonists to a patient with rectovaginal endometriosis, do not expect the same speed of response as in a patient who has superficial endometriosis. She will only start to respond after two or three months. In the future, there will probably be other medications acting on the microenvironment, maybe interferon. It has been shown that interferon can reduce fibroids. Now that we understand that rectovaginal endometriosis is different from endometriosis, we can focus on a different target, the adenomyotic or myoproliferative lesions."

**Dr. Hugo Verhoeven:** "We've discussed the past, so what about the future? What might be the next breakthrough in the diagnosis and treatment of endometriosis?"

**Professor Brosens:** "I think the future will be a non-invasive testing which will make it possible to determine who is an at-risk patient. These patients can then be investigated with high-resolution sonography and MRI. Patients who have problems with infertility should receive very early investigation by techniques of endoscopy that are less invasive than some laparoscopy procedures, such as transvaginal hydrolaparoscopy. This can be done in the office. It has the advantage of being performed with saline distension and not CO2 gas. Looking underwater for adhesions is much more accurate and, therefore, endometriosis can be detected in patients who would otherwise be classified as unexplained infertility cases."

**Dr. Hugo Verhoeven:**
"My final question: are you encouraging early screening for endometriosis? What patients would you encourage to have that screening?"

"As long as we do not know how we can prevent the development of the disease, early screening does not make much sense. But I would say that in a patient who has symptoms, an early diagnosis is extremely important. If a patient has dysmenorrhea, then a non-invasive test to see if she's a candidate for endometriosis would be very useful. Then, if she's positive, the doctor can detect the disease. Today, the interval between the onset of the symptomatic pain and the diagnosis of endometriosis is up to thirteen years, and meanwhile the disease is advancing. Patients who have infertility problems should do the screening in the beginning and, if they are positive, go ahead by performing a transvaginal hydrolaparoscopy. We should try to make the diagnosis much earlier so therapy can be done in the early stages in patients with pain, as well as patients with infertility problems."

Dr. Hugo Verhoeven: "Thank you very much."

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