Dr. Genest: I discovered, I'd say, a subspecialty in medicine that I didn't know about but that is absolutely fascinating. How does the immune system manage to accept a pregnancy for nine months when it is supposed to do the opposite?

Annie DeMelt: Hi, this is Annie deMelt and welcome to this CODE LiFE interview. Today we're going to talk about advances in the field of reproductive medicine. We know that one in six couples in Canada has fertility problems and fortunately, many of them can become parents through artificial insemination or in vitro fertilization. However, for some couples, these treatments don't seem to work at all and we don't know why. The reasons are unknown. Our guest today aims to help these couples become parents. Dr. Geneviève Genest is an immunologist and a researcher at the Montreal General Hospital where she runs a clinic that is unique in Canada. Dr. Genest, thank you for being with us.

Dr. Genest: Thank you for having me.

Annie DeMelt: So I would like to start with the one in six couples who have fertility issues when they come to you. When they knock on your door or you get an email, where are they in their journey when they come to you?

Dr. Genest: Quite far. When we talk about the statistic that one in six Quebecers have fertility problems, it's real, it's huge. But the people who come to me are patients for whom we have no explanation for their repeated miscarriages or their infertility. They've had multiple unsuccessful attempts, had multiple miscarriages with all the medication we have to offer in the regular programs and still have no children. These are patients who have spent several years in fertility clinics, several years having repeated miscarriages and who are really at the end of their rope. Their doctors say 'sorry, I have no explanation for what's going on and you've failed all my treatments. Let's go and see if it's the immune system', so these are patients who are really - not necessarily at the end of their journey, but in trouble. They've been through a lot of ups and downs and a lot of medical procedures, a lot of miscarriages, and a lot of embryo transfers, so pretty far along in the process.

Annie DeMelt: When you said: at the end of their rope. It's at the end of their rope, not just physically, but mentally and emotionally too, I guess.

Dr. Genest: Yes, infertility or repeated miscarriages are a marathon, not a sprint. And then, unfortunately, there are many ups and downs. There is a lot of grieving to do. There are a lot of emotions. They are very vulnerable patients, they are very vulnerable couples. They are couples who see all their friends having children, all their friends talking about babies, talking about motherhood. So that's very difficult to feel and it's very isolating. You feel very alone in all this. So the patients I really see are patients who have made many, many attempts, but above all, who are at a fairly high emotional level when they arrive at the clinic. They're very vulnerable.

Annie DeMelt: What's the theory right now in relation to that? What do you think is going on for those who don't have an answer at the moment?

Dr. Genest: That's an excellent question. In fact, just the fact that as women we are able to have pregnancies is an immunological miracle. If you think about it, the immune system is really there to reject anything that is not ours. But in the context of pregnancy, the uterus is an organ that accepts a fetus where 50% of it doesn't resemble us and allows that fetus to develop into a baby. This is quite an extraordinary phenomenon. If you think about it, the immune system is very important for a normal pregnancy. So during the woman's menstrual cycle, the immune system is called to the uterus and this immune system recognizes the embryo, helps the embryo to implant, helps the embryo to form a placenta, but also says to the rest of the system: don't attack, there's something perfectly normal going on. We think that for some patients who have reproductive failures, so repeated miscarriages or multiple unsuccessful attempts at in vitro fertilization, there is a problem with that process.

Annie DeMelt: Okay, but we don't know exactly what's going on, do we?

Dr. Genest: Exactly, and it's very frustrating because we don't have good animal models and we're not able to take biopsies of the uterus while the woman is pregnant, because we can cause a miscarriage. So there is a kind of black box of immunological phenomena that occur at the beginning of pregnancy that we are not able to go and find as scientists. We can guess what's going on. There is good literature to support the fact that the immune system must grow with the pregnancy and must help the pregnancy throughout the pregnancy, but we don't know exactly what is happening. So for these

patients, we don't have a test to determine that their problem is immunological in origin, and infertility or recurrent miscarriage of immunological etiology is really a diagnosis of exclusion. So we only think about it when the woman has had multiple attempts and is still not pregnant and has failed everything we have to offer. In addition, all the tests we usually do are normal. It's really only at that point that you start to think about a problem with the immune system.

Annie DeMelt: It was also an issue that challenged you on a personal level during your residency and that allowed you to make certain connections that brought you to where you are today. Tell us a little bit about this connection, this personal link.

Dr. Genest: In residence, my husband and I decided that we wanted to have children, so we started trying, but unfortunately we had several miscarriages. It was around that time that I was admitted to the Allergy & Immunology program. About two months later, I was doing a clinic with Dr. Phil Gold.

Annie DeMelt: Who is very renown.

Dr. Genest: He is a very renown. He is an extraordinary doctor and an extraordinary researcher at the Montreal General Hospital. He was running an Allergy & Immunology clinic. He's someone I knew from afar just because of his personality, his scientific knowledge, his publications. I knew him from what he had done before, but he became my mentor or at least my teacher at that time. We had seen a case in the clinic, a woman who had had several miscarriages. I think it was seven or eight miscarriages. I wondered, as a resident in allergy and immunology, what was this patient doing in our clinic? So I went to Dr. Gold and asked: what is this? What are we doing for this patient? He replied: Ah, don't worry, give her intravenous immunoglobulin, you'll see, she'll get pregnant. So that's what we did. We treated this woman with a blood product called intravenous immunoglobulin. And as a matter of fact, she did get pregnant and she was able to keep the pregnancy until the end. From that moment on, I was completely surprised and I discovered, I would say, a subspecialty in medicine that I did not know, but which is absolutely fascinating. How does the immune system manage to accept a pregnancy for nine months when it is supposed to do the opposite? This really touched me, yes, on a personal level, but also on a scientific level. How do you explain this phenomenon?

Annie DeMelt: In terms of immunoglobulin, was that something that was usually given? Because it was a bit surprising to see this woman in an allergy clinic. How did it work for that treatment?

Dr. Genest: There were a few publications in the literature at the time on the use of intravenous immunoglobulins off-label. Intravenous immunoglobulin, if given in large enough quantities, can change the way the immune system perceives its environment. So we think that intravenous immunoglobulin in fertility will restore the immune system's ability to recognize the embryo and help the embryo to implant and not reject it. There was a little bit of literature at that time. Not much. It was an interesting molecule. We had tried it on a few patients, so we had a cohort of fifteen patients we treated with intravenous immunoglobulin because we had nothing else to offer them. In fact, thirteen of these patients became pregnant. So we said okay, we'll continue. One thing led to another, and we ended up with a little more than 100 patients. And 60% of them have babies at the moment.

Annie DeMelt: Wow, so the clinic is unique in Canada. This isn't done elsewhere. Why is that? Is it because it was a new concept to try to do this in a more coordinated, more methodical way? What makes the clinic unique?

Dr. Genest: Well, it's the only clinic in a university centre in Canada that does immuno-fertility, with an immuno-allergist who deals with fertility problems. It's also a unique clinic because we deal with all the fertility clinics in Quebec and obstetrics centres in Quebec. It's really a referral centre for patients whose treatments have all failed, for whom their doctors have nothing else to offer. We take these patients into the clinic. It's also unique in Canada because there is no training. When I was looking for training before I could start practicing, it was impossible. There is no centre that offers this training. So I had to look for small parts of different training courses to be able to do what I wanted to do.

Annie DeMelt: But now, is this something you offer?

Dr. Genest: Exactly. So for the last three years, we have had a fellowship program for reproductive immunology. We take residents in allergy & immunology, and soon in

internal medicine and fertility, and we teach them a bit about the theory behind it and what molecule can be used to promote outcomes in patients who are infertile or have repeated miscarriages.

Annie DeMelt: You have someone in Quebec City, if I'm not mistaken.

Dr. Genest: Yes, we have a fellow at the moment who is on maternity leave, so that's coming soon. She was pregnant until yesterday, I don't know if she had her baby since yesterday or not. She's an internal medicine resident who did her allergy & immunology rotation, who is interested in reproductive immunology. She's doing her fellowship with me for, well, she's got six months left, and then she's going to become my counterpart in Quebec. So there will be two of us in Quebec doing this. We're going to be able to collaborate on research projects, we're going to be able to share patients and our knowledge. I hope that, if everything lines up, we'll be able to do this with residents across Canada to bring expertise to other provinces as well.

Annie DeMelt: We've talked about luck, if you will, leading to discoveries. The pandemic was a challenge for many people, including at the clinic. What did the pandemic mean to you? And what opportunities did it bring you?

Dr. Genest: That's an excellent question. So, during the pandemic, we never stopped working. We continued to have all our patients in person, through telehealth. We never stopped our activities, so we were able to continue that. It was really incredible. We adapted like everyone else. The big problem with the pandemic was that there was a shortage of blood donors. This means that blood products are scarcer and must be reserved for patients who absolutely need them. During this time, the government decided to reserve intravenous immunoglobulins for certain patients and prohibited the off-label use of immunoglobulins. So we didn't have access to it for patients with fertility problems for two years. We were able to lobby the government to obtain intravenous immunoglobulin, which we have had since 3 January 2023, but during the two years of the pandemic, we had to find other solutions. It’s going back to the literature, going to other clinics, what are they doing? What molecules to use? What tests to do? We managed to find several molecules that we could use for these patients during the pandemic. And we realized that there were some molecules that worked very well and that we might not need intravenous immunoglobulin. What the pandemic allowed us to

do was to go back into the files of all the patients who had been treated at the clinic to see how many had live births with immunoglobulins or with other treatments such as cortisone, Plaquenil and other treatments that are given in other clinics. We realized that these treatments resulted in live births. At the moment, the criteria to use immunoglobulins is to have failed other simpler treatments before going through this.

Annie DeMelt: There would be simpler options before requiring immunoglobulin.

Dr. Genest: Yes, exactly. Maybe with fewer side effects, less expensive treatment. Because for an intravenous immunoglobulin injection, you have to stay in the clinic for 4 hours. That's half a day's work lost to receive intravenous immunoglobulin, whereas other drugs can be given orally, for example. That’s a home treatment.

Annie DeMelt: So we have a problem and then we have some solutions that seem to work well. What is missing? It's the link between the two that's missing, it's the test. What are you doing at the moment to try to figure that out?

Dr. Genest: That's another excellent question. Because the problem, when we have a couple like that who come to the clinic, is that we don't have any tests to say that your problem is immunological, here is the molecule that will help you best. Or conversely, you *don't* have an immunological problem. Go look elsewhere, you're wasting your time in my clinic. If we're not able to do that, then we can guess what the patient needs. So yes, we guess very well, we do tests, we look at the patient's history, we talk to our colleagues, we make scientific hypotheses, so to speak, but the fact remains that we don't have tests to direct our treatments and therefore we don't have the possibility of offering personalized medicine. Which is what would be appropriate for these patients who are really at the end of their rope. What we do to remedy this is to include all the patients who come to the clinic in a registry, so that we can document which molecules they received. What are the outcomes? What are the side effects? Were they able to have a baby or not? The other thing we're doing is taking blood samples before and after treatment to try to see if there are differences in the immune system between patients who are successful with these treatments and patients who are not, versus patients who are able to have babies without treatment. We're trying to see: Is there an immunological difference between these patients to see if we could develop a test, eventually, to diagnose infertility or recurrent miscarriages of immunological origin.

Annie DeMelt: Really, the blood test would make all the difference, is that right?

Dr. Genest: I think so. Well, at least being able to determine whether the problem is immunological in the first place to be able to better define the treatments. So at least starting with that, will already be huge.

Annie DeMelt: For you and for the patients too, to get answers.

Dr. Genest: For patients especially, to get answers. Because the big problem in unexplained infertility or unexplained miscarriages is really that, it's unexplained. So I find as human beings, we always try to have explanations, we try to explain everything and when, as a couple, we are not able to have babies, but everyone around us is able to have babies… We have tried everything to have a baby and we still can't, not knowing why is very difficult, it's very isolating. So even if we're able to say to them, "Well, here's your problem, it's an immunological problem, here's how I can treat you", that helps a lot. On the other hand, to say it's not an immunological problem, you don't need my treatments, that helps a lot too.

Annie DeMelt: How could we better support you in what you do? Because you are very personally invested in this, but you need infrastructure if I am not mistaken.

Dr. Genest: It's really the infrastructure that we need. First of all, we need someone on the floor, so we need a nurse, even a part-time nurse, a nurse who is really dedicated to this clinic, who can answer patients' e-mails, who can schedule patients, who can order tests. Sometimes, you know, we have patients who come in with a new pregnancy, but we have to do the tests, we have to send them to consultants, we have to monitor the medication. Having someone to coordinate all that will allow us to see many more patients. Because right now, I'm the one who does all that, the patients send me emails directly. Eventually, if I want to see more patients, we really need this infrastructure to be able to take care of the patients we have. We also really need a research nurse to make sure that the samples get to their destination, to handle the samples in the laboratory, to make sure that all the patients are entered in all the databases, to coordinate with other clinics, and eventually to build a pan-Quebec, pan-Canadian network. It's also about having a research coordinator to help us with all that. So really,

that's the key right now, it's really the infrastructure to allow us to see more patients and have more impact, to train more people.

Annie DeMelt: What do you hope for your patients? For the couples who will come to see you in the future. We talked about more specialized medicine and more precise tests. What direction do you think we're heading in? What is your hope for those people who are having fertility problems at the moment?

Dr. Genest: I hope that we are moving toward a diagnostic test. I think we'll be able to do it. The diagnostic test is very, very important. But what I hope for these couples is that they don't lose sight of each other during the process because it's so easy. There's a lot of stress, a lot of emotion, and a lot of grief to go through. Sometimes patients are so invested in the process and in explaining the thing that they forget to focus on themselves as a couple. There's a very high rate of divorce, of separation, among couples who go through things like that, just because that's what it is, we lose sight of each other, we medicalize the thing too much. It's really about taking responsibility off the couple, to say *it's not your fault, there is a medical problem*. It's not your fault if there is a medical problem. It's our fault if we are not able to find it. So help us find the medical problem, wait for us to do the assessment and then we'll be able to help you. For the vast majority of these families, we will be able to give them a child, but sometimes it just doesn't work. At that point, being able to say that to a couple, to say: it won't work naturally, let's look elsewhere. Egg donation, surrogate mothers, adoption. That's also therapeutic because then, we leave that project and we're able to concentrate on another project together.

Annie DeMelt: Thank you very much, Dr. Genest. Wow, it's powerful to say it's not you, it's us who don't have the answers yet. Thank you very much for your time. Thank you for what you do. You are obviously very much appreciated. Thank you for listening to this CODE LiFE interview presented by the Montreal General Hospital Foundation. To learn more about Dr. Genest's research and other initiatives supported by the generosity of our donors, you can visit the CODE LiFE Foundation's website. You can also follow us on social media and don't forget to subscribe to the podcast for more CODE LiFE interviews. Thanks again and see you next time.