

Announcer: Welcome to Medical Breakthroughs from Penn Medicine, Advancing Medicine Through Precision Diagnostics and Novel Therapy.

Dr. Caudle: This is Medical Breakthroughs from Penn Medicine on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me on this episode are two of the investigators of the UNTIL trial at Penn Medicine. We have Dr. Kathleen O'Neill. She's Co-Lead Investigator and Assistant Professor of OBGYN. She's also a reproductive medicine specialist, and we also have Dr. Nawar Latif. He's a Co-Investigator and Assistant Professor of OBGYN. He's also a gynecologic oncology surgeon. Dr. O'Neill and Dr. Latif, welcome to the program.

Dr. O'Neill: Thank you for having us, Dr. Caudle.

Dr. Latif: Thank you.

Dr. Caudle: Absolutely, really excited to hear about this program and to hear your perspectives. So first to start off, Dr. O'Neill, why don't we start with you? Can you tell us a little bit more about what uterine factor infertility, or UFI, is?

Dr. O'Neill: Of course. We see patients in the infertility clinic that have a number of etiologies, can be male factor, can be related to age-related infertility, can be tubal factor infertility, and some women are unable to carry a pregnancy either because they are, do not have a uterus or because they have a uterus but the uterus is not functional, and you can either not have a uterus because it was removed for something like cervical cancer or after an obstetric complication or there's a condition where women are born without a uterus that affects about 1 in 4,000 women called Mayer-Rokitansky-Küster-Hauser syndrome, or MRKH, so we, and we see individuals with uterine factor infertility not infrequently in, in the clinic.

Dr. Caudle: Interesting. That's very interesting, let's dive into the UNTIL trial. So, Dr. O'Neill, back to you, what did this trial focus on, and really how was it designed?

Dr. O'Neill: If individuals with UFI want to achieve parenthood, they have two options right now. They can use a gestational carrier or they can adopt, and if they want to have a child that's genetically related to them or their partner, the only option is use of a gestational carrier, and these are alternatives. I'm incredibly glad that they exist for my patients, but women had voiced and couples had voiced that they were alternatives and not really treatments for uterine factor infertility, and they didn't allow them the ability to carry a pregnancy, which was important to some, to some individuals.

So, out of those kind of out of the feeling that the options that these women had were insufficient in some ways, this idea of uterus transplant came about, and basically just in broad strokes, when we do a uterus transplant, we take the uterus and the cervix and the top of the vagina and connect it in the recipient, and so in order to achieve pregnancy, you have to put an embryo directly back into the uterus. These women have functional ovaries. They are able to go through in vitro fertilization and create embryos, so they do that process first.

They then have their uterus transplant and start on an antirejection regimen, and then if they, if the transplant is successful and they are stable for six months, we begin attempts at pregnancy by putting an embryo back in the uterus one, one at a time. Hopefully they achieve pregnancy, and we deliver them by C-section at 37 weeks ideally. They were allowed up to two live-born children in the trial using the transplant, and then, unlike any other organ transplant, at the end of their childbearing, we remove the organ, we remove the uterus, and that allows them to stop the antirejection medication so they're not on that for an extended period of time.

Dr. Caudle: That's interesting, and, and it's really helpful for you to explain that. Before we get to you, Dr. Latif, or maybe both of you might want to chime in on this, I'm just curious because you mentioned you know, the need for another option besides the two options that had previously existed for women who wanted to bear children in this situation, when, around what year did we start thinking about uterine transplants? Like, how recent or new is this as a concept?

Dr. O'Neill: It, it actually started in the 1970s, but then in 1978 IVF became a, a treatment. And a lot of focus went to that. So, it didn't grab attention again until the 90s. And there were a couple of uterus transplants. There was one in Saudi Arabia, the first one in 2001, and then there was one in Turkey in 2011, but where it really started picking up steam was a trial that started in Sweden at the University of Gothenburg led by Mats Brännström, who is both a gynecologic oncologist and a reproductive medicine specialist, and he started a trial using living donors in 2012 or 13, and the first live-born child I believe was in 2014 or, or 15, and so after that excitement really spread, and programs started around the world.

Dr. Caudle: Mm, that's really interesting, very interesting. So Dr. Latif, let's go to you for a second. Can you talk about how patients are identified as candidates for, for this trial?

Dr. Latif: So, patient can apply through, for the UNTIL trial through the website, through, and, once we launched the website and the, launched the trial, we have tremendous, interest in, the trial. We go through the applications and we also review the medical records of each applicant and go through the inclusion/exclusion criteria for the for those applicants, and then after that we, see those applicant that we feel that that they are that they are basically fill the, the inclusion/exclusion criteria and see them and not, those who see them usually, the transplant surgeon, Dr. Paige Porrett, me and Dr. Kate O'Neill, and also psychologists, pharmacists. We have many specials who would evaluate those applicants to make sure that they fit into the, the, into the trial.

Dr. Caudle: Yeah, very interesting. It sounds like a very multidisciplinary approach, which makes a lot of sense.

Dr. Latif: Yeah, we, we, I think we have more than 30 specialists in, in this trial that all participates, during the process from the first time the patient, the applicant apply to the program, until we, where we are right now.

Dr. Caudle: Wow, that's interesting. So, you know, let's talk about, the global scope of, uterus transplants. You know, the majority of the world's uterus transplants, and apparently there have been more than 70 at this point, which is really amazing, have really been performed with living donors. So, Dr. Latif, can you tell us if there's some advantage to living donors in the context of uterine transplant?

Dr. Latif: At this point, as you said, the vast majority are, of the uterus transplanted are from living donors, and then we think that the living donors, one of the advantages are, is we can vet those, applicant for the transplant. We, basically do a lot of testing, imaging testing to evaluate the vasculature, because that's one of the most important things in the uterus transplant, the arteries, the vein, more specifically, the, the internal iliac artery and the internal iliac vein, the benefit is that we will be able to select the really good candidate that can increase the success of uterus transplant. The other benefits of the living donor is that we can also have, know the background and the history of those patient. The difference for, from the living donor compared to deceased donor is that sometimes with the decreased donor of uterus transplants we have sometimes limited information about the background, the history, the medical history of those patients.

Dr. Caudle: Yeah, that makes a lot of sense as well. Dr. Latif: I would like to add that, however, that at Penn, the first two uterus transplant were from deceased donor.

Dr. Caudle: Interesting. What is of the 70 roughly cases that have, uterine transplants that have happened throughout the world, can you give me an idea of what percentage have been from living versus deceased donors?

Dr. O'Neill: I think 75 percent is the, is the most accurate estimate.

Dr. Caudle: For living donors?

Dr. O'Neill: For living donors.

Dr. Caudle: So, that's by far most common.

Dr. O'Neill: Yeah, and, you know, around the world, the use of a compensated gestational carrier in many countries is illegal. So, I think that that's something that a lot of people even in the United States don't realize. The use of a compensated gestational carrier, which is the predominant form, the, the other alternative being, like, a sister carrying a pregnancy for you, which is obviously not compensated, but in the, in the United States even, compensated surrogacy is the, is more common more common type of, type of a gestational carrier, and it is explicitly illegal in the United States in six states, one of those states being New York. So, if I have uterine factor infertility and I want to find a compensated gestational carrier, I have to leave the state because I cannot participate in that relationship, and a medical professional cannot facilitate that.

On first offense, it's a fine, and on second offense it's a felony. So, as much as people love their patients, they're not willing to sacrifice their medical license to help them set up that, that arrangement, and I think people really don't realize that. They say, "Why don't you just adopt? Why don't you just have someone else carry the pregnancy for you?" And they don't realize that that's not necessarily an, an accessible option depending on where you are in the region or depending on what your financial means may be.

Dr. Caudle: Right, and just, and that's fascinating, had no idea about that, and just to clarify for our listeners and myself, compensated – you mean financially compensated, I'm assuming?

Dr. O'Neill: Right.

Dr. Caudle: So, you're paying someone to carry the child as opposed to what you mentioned, the sister being someone that's...

Dr. Caudle: Offering to do it or, you know, that's interesting, so six states it's illegal.

Dr. O'Neill: Right. Six states it's illegal. In some states, it is legally protected. But in the vast majority of states, there really isn't a legal protection. So, if you set up a contract with a carrier saying, "I'm going to be on the birth certificate, I'm going to be present at all the ultrasounds," and for some reason there's deviation from that, you don't really have necessarily a legal recourse to get that contract enforced. So, it's just, it, there's risk. And with this being, you know, your child, it's an unacceptable risk for some individuals.

Dr. Caudle: Absolutely, no, that, that makes a, a lot of sense, and I think that's very helpful background information. You know, let's go back to the trial, the UNTIL trial, Let's take a look ahead at this groundbreaking trial, which it really is.

Dr. O'Neill, what's really next for the UNTIL trial at Penn?

Dr. O'Neill: As Dr. Latif said, our first two transplants were using a uterus from a deceased donor, and we are now moving into the phase where we have received a lot of applications from living donors who are interested in participating. So, the next on the clinical side, the next phase is moving into, some living donors, and hopefully we can get more information about if one source of a donor is better than the other, if the outcomes are better with one or the other. So that's on the clinical front, and on the research front, so, Dr. Latif mentioned my co, my co-principal investigator, Dr. Paige Porrett. With her we're looking at a lot of really outstanding fundamental questions about transplant, about pregnancy, and about this phenomenon of immune tolerance.

How does a woman's body accept a growing pregnancy, which is half her and half Dad? That's a phenomenon that is not really well understood, and we're hoping that not only is this trial going to benefit the individuals who participate and hopefully that they will have, be able to carry a pregnancy and have live-born child but will also benefit, you know, the world at large because we'll be able to get some more information about some of those fundamental questions that could impact not just women, not just babies, but actually men, also, transplant recipients, that kind of thing. So, it's really a push on the clinical side for the living donor trial and also a push on the research side to learn as much as we can. I think that's one of the responsibilities of innovation is that not just that you drive one particular asset, but you think about the ways in which it can impact medicine at large.

Dr. Latif: And I would like to add that on the clinical aspect and the living donor transplant surgery, we our, our goal is to basically do these surgeries, the living donor surgery robotically with the goal is that and this is like another step or a next level of complexity the surgery, but this will benefit the donors. This donors are not compensated, so we, and obviously we're trying to minimize their risk to almost none from the surgery and also minimize their downtime, so their healing time and that's why we feel that the future for living donation, the trust living donation going to be robotic surgery, and that's one of the, like, the next things that we are doing here, which is doing robotic living donor surgeries of, and that we believe that's going to help in terms of the surgical aspect of the actual surgery itself and also for the healing and the recovery time for the donors.

Dr. O'Neill: Dr. Latif has been pushing for that since day one. Can we do it with a minimally invasive approach? And the other, I want to add one other thing – the other thing that we're hoping to improve from this trial is awareness, right? So, letting people know that this condition exists, first of all, women are born without a uterus, and also just in infertility in general, raising infertility in, awareness about infertility in general. It has been a bit of a taboo subject. Some people don't want to talk about it, and I think that, that harms the kind of community at large because it, it keeps it in the shadows.

We want to talk about how this exists, how women and men value their family and family building. This should be a priority for us, and as a result of that, we should put resources behind that, healthcare resources, communicate that that is important to your employer, to your congressperson, to your senator so that we can start getting more coverage for fertility care. I think that's a huge component of our responsibility is to be advocates for these individuals because we meet them, and we hear their stories, and I think they're, they're very powerful.

Dr. Caudle: That's so interesting. It's so nice to hear you both talk about not only, you know, the research that you're doing that affects a very specific population in many ways, but, you're talking about how it really can change the world at large, right? Even to advocacy and, resources it's very exciting. Lastly, I'd really love to hear from each of you on what implications you think the UNTIL trial will have on the future of medicine, and Dr. Latif, maybe we'll start with you.

Dr. Latif: Yeah, I think from, as a GYN oncologist from the GYN oncologists' perspective, we we see many patient, and especially young patients women with the cancer, and unfortunately part of the treatment for cancer, for gynecologic cancer is removal of the uterus. So, I think one part of what I see the future coming is that we can offer this option for women who lost their uterus for for cancer in the future. , obviously, this is still a research area, and we work, still working on it, but I think the next five to ten years, I think this is going to be one of the option that we part of the standard of care we offer to patients. , the other thing I'm passionate about is that I'm I'm more passion about surgical education and, and, and training, and I think in the future for GYN oncologists is going to be part this type of surgery is going to be one of the highlight or the interest of training that we can offer for trainee in this field which is very unique surgery that I think in the next five to ten years is going to be more common, and the requirement for multidisciplinary surgeons to do this type of surgery will be a requirement for a success of such a program.

Dr. Caudle: Hm, that's interesting. Yeah, that's great. Dr. O'Neill, what about you? Any final thoughts about this?

Dr. O'Neill: I'm going to, I had the advantage of going second, so I get to piggyback after, off Dr. Latif's response a little bit. I think if I had to think of, like, three key words with this trial and with uterus transplant in general, I think it's, they would be collaboration, hope, and choice. So, this would not be possible, as Dr. Latif said. I think at our last count, there was over 130 people on this team, so it would not be possible without someone from seemingly every department in this hospital – transplant, radiology, psychiatry you know, OBGYN. It, it just wouldn't be possible, so I think it's been a huge, huge exercise in collaboration and how people work together and how people can learn from each other. The other thing is, this is, like Dr. Latif said, it's a research trial right now, but I think even the existence of this as a research trial and hopefully as clinical care moving forward if, in fact, the outcomes are, are good as we think they will be it's, it's gives women hope and a choice.

These women often come in, women that are born without a uterus come in, you know, in their teen years because they haven't had a period, and we do an exam and tell them, "You haven't had a period because you don't have a uterus, and so not only are you not going to have periods like your friends and how do you wrap your head around that, but if you're interested in having children, which you haven't even begun to thought, think about because you're 15, you're not going to be able to."

And same thing for individuals who had cervical cancer. You know, they're concerned about their life and so they have surgery, and then all of a sudden they have this other element of their life that in some way they feel has been taken for, from them. So, I think saying there is this potential choice for you, and it's a source of hope, so even if you don't end up pursuing it, knowing that it exists in the event that you want to, I think gives women a sense of control in a, in a situation where they feel everything is very out of their control. So, I think those are kind of the things that I think about that make this worth doing and why, you know, Dr. Latif, Dr. Porrett and I pour our time into it, really, and the other 130 individuals that we are very grateful to.

Dr. Caudle: That's excellent. You know, the passion that both of you have is, is palpable. It's, exciting as another physician, to hear about this, which, as a family doctor, this is new to me, so I'm sitting here learning like the rest of our listeners. So, I'd really like to thank you, my guests, Dr. Kathleen O'Neill and Dr. Nawar Latif, for sharing their insights on this truly remarkable trial and how it will play a role in the future of medicine. It was really great having you both on the program.

Dr. O'Neill: Thank you so much.

Dr. Latif: Thank you for having us.