Melanie Cole, MS (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Colan. Joining me today to talk about IVF and male factor infertility is Dr. Christine Skiadas. She's the Medical Director of Penn Fertility Care at Lancaster General Health. Dr. Skiadas, thank you so much for joining us today.

A recent consensus report from the Journal Nature suggests that there's been a rapid decline in male fertility worldwide in recent years. Do you know why this has been happening?

Dr. Christine Skiadas: Thank you for the opportunity to speak with you today. Human fertility is a complex process, and we are seeing worldwide that the rates of births per woman, which is often used to define the rate of fertility, has been declining. However, this decline is likely related to multiple factors, both on the male and female side, including contraception as well as changing social dynamics, ideal family size, and couples pursuing pregnancy at older ages than they were, say, 50 to 100 years ago.

That being said, we have seen consistent reports to indicate declining sperm parameters over the past 50 years, studies that have actually been done around the world. Although we don't know exactly why these counts have been declining, there are several candidate factors, including environmental exposures, lifestyle factors. And some of the areas under active investigation include the impact of medical conditions, including obesity, exposure to alcohol or nicotine, as well as cannabis, and environmental disrupting chemicals such as endocrine disruptors, which could also be playing a role.

Melanie Cole, MS: Such a multifactorial situation. And thank you for those statistics. And among patients in the Nature Review is that many of the criteria used to determine infertility in men, sperm count and hormone profiles, as you were just saying, for example, have not changed substantially in more than 50 years. What's evolving in the science of male infertility diagnostics and the cause of male infertility?

Dr. Christine Skiadas: I think across the field of medicine, where we're seeing the most rapid expansion in terms of diagnostic testing is within the field of genetics. And I think that this likely represents the greatest area of opportunity for diagnostic testing in the future. Although we have some known genetic causes of male infertility, such as chromosomal variants, Y chromosome microdeletions, and genetic mutations in the cystic fibrosis gene, for example, that can lead to congenital absence of the vas deferens, there are many more

genes involved in spermatogenesis that likely will be identified and become commercially available for testing in the future.

One of these potential benefits of having improved insight into genetic causes is that it would potentially help us identify which couples should think about moving to assisted reproductive technology sooner and which couples may have a greater likelihood of responding to changes in their lifestyle or modification of environmental factors.

Melanie Cole, MS: Dr. Skiadis, I'd like you to speak about patient selection here. When is IVF recommended for male factor infertility and how do you determine which of the many available options to use?

Dr. Christine Skiadas: IVF has revolutionized the treatment of infertility in general for both female and male factors, but certainly is a procedure that we only do after an extensive discussion with a couple about their prior diagnostic evaluation, as well as trying to optimize their natural fertility. For example, for any patient who has a severe male factor identified, which typically, as you mentioned earlier, is diagnosed on a semen analysis, an initial evaluation would include a thorough exam by a reproductive urologist as well as potential additional diagnostic tests including hormonal profiles, possibly a scrotal ultrasound, or additional testing about his other medical conditions.

Thankfully, we have a wonderful reproductive urologist who we work with to understand if there are other health issues leading to a low sperm count. In addition to potentially identifying obstructions in the vas deferens, identification of varicocele, or varicose veins in the scrotum which could be causing abnormalities in the sperm counts, I've had patients diagnosed with testicular cancer, profound thyroid disorders, or even diabetes as part of their initial fertility evaluation.

If we find a correctable cause or some other medical condition, trying to optimize the treatment of that first and seeing if that would have any impact on the semen parameters is often the first goal to see again if we can improve natural fertility. However, if it's not possible to improve the sperm count, then we will often discuss IVF, particularly when the total number of swimming sperm is less than 10 million. Depending on the semen parameters, there are two methods of fertilization that can be used with IVF, the standard of which is called conventional insemination, where a droplet of sperm is just mixed with the egg, as opposed to intracytoplasmic sperm injection, which is often done for more severe male factor infertility to inject a single sperm into each egg.

Melanie Cole, MS: Doctor, you do ICSI, as you just mentioned, intracytoplasmic sperm injection. It's one of the available procedures at Penn Medicine for men. And as you just said, it involves injecting sperm into an ovum. But what can you do if no sperm are available in the instance of vasectomy or other types of sterilization, or if the available sperm are found to be abnormal for physical or genetic reasons? So then, what's the next step there?

Dr. Christine Skiadas: In those situations, we do need to ideally have known sperm available prior to having the female partner undergo controlled ovarian hyperstimulation. So for patients who've had a vasectomy, they often can have a sperm aspiration procedure from the epididymis, again performed by a reproductive urologist, and that sample can be cryopreserved in the laboratory in order to then be warmed and have sperm available for injection on the same day that female partner would undergo an egg retrieval.

Melanie Cole, MS: IVF has been known as an expensive undertaking. Dr. Skiadis, can you discuss the many ways that Penn Medicine assists couples, men and women, seeking fertility care?

Dr. Christine Skiadas: We have a dedicated financial advocate who is able to work with every one of our patients to understand if they have any insurance benefit for fertility care, as well as to discuss the approximate costs, as well as financing options that may be available. Thankfully, fertility insurance coverage is expanding in the United States. There are several states where there are mandates for fertility coverage. Pennsylvania is not yet one of them, although there are many employers within the state who have gone out of their way to provide insurance coverage for their employees to be able to access fertility care, including Penn Medicine as an employer.

Melanie Cole, MS: Doctor, finally, how would referring physicians or other interested parties reach out to Penn Fertility Care and what would you like them to take away from this episode about male infertility and the options available at Penn Fertility Care?

Dr. Christine Skiadas: Penn Medicine has been a longstanding leader in fertility care. The program in Philadelphia has been one of the oldest and most highly regarded programs, and it was actually my exposure to their team as a medical student that led me to pursue reproductive medicine. I'm delighted that we're able to now offer comprehensive reproductive care also at Lancaster General Hospital to our patients in this community. And we can be found at lancastergeneralhealth.org/fertility or by doing any Google search for Penn Fertility Care would bring you to either the Philadelphia team or our team in

Lancaster. People thinking about referring patients for male infertility should keep in mind that young men as a group are a group of patients that probably are underutilizers of healthcare. And so, if a younger man is in the office of a primary care physician, having at least some discussion of reproductive goals and trying to modify lifestyle factors and optimize general health to preserve fertility would be a great starting point in terms of conversation. And again, for any couple that has been attempting pregnancy for more than a year without success, a comprehensive fertility evaluation can lead to a lot of insights as to how to help them achieve their reproductive goals.

Melanie Cole, MS: Thank you so much, doctor, for joining us today. That was such an informative episode. To refer your patient to Dr. Skiadis at Penn Medicine, please call our 24/7 provider-only line at 877-937-PENN, or you could submit your referral via our secure online referral form by visiting our website at pennmedicine.org/refer-your-patient. That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole.