Hormone Usage & Cancer Part 2:

Hormone Usage for Fertility Before, During, and After a Cancer Diagnosis

National Webinar Transcript

August 11th, 2022

Presented by:

SHARSHERET®
The Jewish Breast & Ovarian Cancer Community

About Sharsheret

Sharsheret, Hebrew for “chain”, is an international non-profit organization, that improves the lives of Jewish women and families living with, or at increased genetic risk for, breast or ovarian cancer through personalized support and saves lives through educational outreach.

With regional offices in the Midwest, Northeast, Southeast, West, and Israel, Sharsheret serves 275,000 women, families, health care professionals, community leaders, and students. Sharsheret creates a safe community for women facing breast cancer and ovarian cancer and their families at every stage of life and at every stage of cancer - from before diagnosis, during treatment and into the survivorship years. While our expertise is focused on young women and Jewish families, approximately 25% of those we serve are not Jewish. All Sharsheret programs serve all women and men.

As a premier organization for psychosocial support, Sharsheret works closely with the Centers for Disease Control and Prevention (CDC) and participates in psychosocial research studies and evaluations with major cancer centers, including Georgetown University Lombardi Comprehensive Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

Sharsheret offers the following national programs:

The Link Program

Peer Support Network, connecting women newly diagnosed or at high risk of developing breast cancer one-on-one with others who share similar diagnoses and experiences

- Embrace™, supporting women living with advanced breast cancer
- Genetics for Life®, addressing hereditary breast and ovarian cancer
- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors
- Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- Family Focus®, providing resources and support for caregivers and family members
- Ovarian Cancer Program, tailored resources and support for young Jewish women and families facing ovarian cancer
- Sharsheret Supports™, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia, on issues unique to younger women facing breast cancer
- Sharsheret on Campus, outreach and education to students on campus
- Sharsheret Educational Resource Booklet Series, culturally-relevant publications for Jewish women and their families and healthcare Professionals

Disclaimer

The information contained in this document is presented in summary form only and is intended to provide broad understanding and knowledge of the topics. The information should not be considered complete and should not be used in place of a visit, call, consultation, or advice of your physician or other health care Professional. The document does not recommend the self-management of health problems. Should you have any health care related questions, please

call or see your physician or other health care provider promptly. You should never disregard medical advice or delay in seeking it because of something you have read here.

The information contained in this document is compiled from a variety of sources (“Information Providers”). Neither Sharsheret, nor any Information Providers, shall be responsible for information provided herein under any theory of liability or indemnity. Sharsheret and Information Providers make no warranty as to the reliability, accuracy, timeliness, usefulness, or completeness of the information.

Sharsheret and Information Providers cannot and do not warrant against human and machine errors, omissions, delays, interruptions or losses, including loss of data.

Eve Kleinerman:

Good evening. Thank you, everyone, for joining us for this important program this evening on hormone therapy. My name is Eve Kleinerman, and I am the Sharsheret Illinois regional director. Tonight, we are going to be learning from Dr. Jovana Lekovich about hormone therapy as it relates to fertility preservation in cancer patients prior to the start of treatment, as well as those pursuing family or infertility treatment for survivors of cancer. We are grateful for tonight's webinar sponsor, Merck, and it is thanks to their support that we've had this two-part series focused on hormone therapy. For those who are not able to join us for the first part, our recording from that webinar is available on Sharsheret's website.

And before we begin, I do want to cover a few housekeeping items. Today's webinar is being recorded and we'll be posted on Sharsheret's website along with the part one recording as well. Along with the transcript of the webinar, participants' faces and names will not be included in the recording, but if you would like to remain private, you can right now turn off your video and rename yourself or you can call into the webinar and instructions are in the chat box now for both of those options. You may have noticed that you were muted upon entering the Zoom. Please stay muted during the call and if you do have any questions, feel free to send them in the chat box either to Sharsheret or to myself. And we will have Dr. Lekovich address those questions at the end during the question and answer. We do recommend that you keep your screen on speaker view as this will enable you to see the presentation more clearly and you can find this option in the upper right-hand corner of your screen.

As I mentioned before, today's webinar is part of a two-part series on hormone usage. Tonight is part two, and we are focusing on hormone therapy as it relates to fertility preservation and cancer patients prior to the start of treatment as well as for those who are pursuing family or infertility treatment for survivors. For those who are interested in part one of the series, the link is in the chat box now.

As we move into the webinar itself, I also want to remind you that Sharsheret is a national not-for-profit cancer support and education organization and does not provide any medical advice or perform any medical procedures. The information provided by Sharsheret is not a substitute for medical advice or for treatment for specific medical conditions. You should not use this information to diagnose or treat a health problem. If you have any questions that are specific to your medical care, you may be advised to speak with your medical provider. Always seek the advice of your physician or qualified healthcare provider with any questions you may have regarding a medical condition. Now, before we begin the program, I wanted to introduce Alona who will be sharing her story with us.

Alona Shaked:

Hi everyone. Can you hear me? Perfect. Yes. So thank you so much, Eve, and thank you so much to Sharsheret. My name is Alona Shaked. I live in Philadelphia now. I was diagnosed with breast cancer when I was 28 years old. I was living in Los Angeles at the time and I didn't know anything about breast cancer. It turned out I was BRCA1 positive, which I did not know, but I just happened to find a lump in one of my breasts and went in, and three days later I got a phone call. So at that time, it was almost exactly 10 years ago that I was diagnosed. I was not given many options for fertility preservation, and at first, there were no options given for fertility preservation other than a shot called Lupron, which was supposed to shut down my ovaries so that hopefully they would be preserved and work again after treatment.

But I did a little research and I found that other people were freezing their eggs before chemo, so I pushed back a little bit and my oncologist ended up agreeing to let me do one cycle of egg freezing. So my cancer, by the way, I had three tumors, two of them were triple-negative and then one of them was slightly hormone positive. So that was the concern, the hormone positivity. So I went through the cycle.

It was really, really tough and unfortunately, it was mostly unsuccessful. We ended up collecting five eggs total, which for someone who's 28 wasn't a great number. But at the time I was single, I hadn't really started thinking about my family planning, so I just let that go for then and I focused on beating breast cancer, which I did, thank God. So fast forward a couple of years, I ended up getting married to my wonderful husband when I was 35 and we immediately started trying for a family because I knew that there were going to be some issues and nothing was happening.

So after a few months we went to see a fertility specialist and they did see that there had been some damage to my reproductive system. It turned out there was a whole lot more including male factor, which that's something that is a whole other issue. But I had to go through three rounds of IUI, five rounds of IVF. I actually did a total of eight retrievals, which if anyone's been through an egg retrieval and knows that that's not fun. And finally on my last cycle we got three PGT, a normal embryo, which means they were chromosomally normal. And last November I gave birth to my miracle daughter at the age of 37. She's just sleeping in the next room. I just put her down. So hopefully she stays asleep. I mean, we are now gearing up to think about having a second child. It's very complicated. I have now removed my fallopian tubes because of the BRCA gene, so IVF is now my only option.

Probably many of you know this is not covered by insurance. There are a lot of complicated factors that go into this, whether to test for the gene, that's another issue. We did not test my daughter for the gene because we just didn't have enough to test with. So there's a lot of bioethics involved as well. But that's my story in a nutshell. And if anyone is interested, I have a blog, and I'll just put a link to that in the chat where you can read more specifically about my story if you're interested in that. And I'm more than happy to connect with anyone who's going through this because I've definitely been through it and I'm always happy to talk to other people who need support. So thank you so much.

Eve Kleinerman:

Thank you, Alona. We really appreciate you sharing your story and it was so meaningful to hear this evening on this topic. And now, I am honored to introduce Dr. Jovana Lekovich. Dr. Lekovich is a double board-certified obstetrician and gynecologist and reproductive endocrinologist, and infertility specialist who leads RMA of New York, Brooklyn as its medical director. She's the director of the Oncofertility Program at the Blavatnik Family- Chelsea Medical Center at Mount Sinai. Dr. Lekovich is an assistant clinical professor at the Icahn School of Medicine at Mount Sinai in New York. She specializes in treating all aspects of reproductive medical conditions, including fertility preservation, ovulatory dysfunction, amenorrhea, polycystic ovary syndrome, age-related fertility decline and diminished ovarian reserve with ovulation induction, intrauterine insemination, and in vitro fertilization, intracytoplasmic sperm injection and pre-implantation genetic testing of embryos. Dr. Lekovich's special scientific and clinical interests include preventative and medically indicated fertility preservation and LGBTQ+ family-building. Dr. Lekovich, thank you so much for being here and the screen is all yours.

Dr. Jovana Lekovich:

Thank you so much, Eve. Now that you say it, it sounds so horribly complicated and it sounds like so much. But the truth is, and I was just thinking about it recently, the interesting fact is that it does really take longer to train a reproductive endocrinologist than a cardiologist. And it really is an interesting fact because the reproductive system is complicated, and in my opinion and in the opinion of our scientific community, it really is what keeps the planet going. Yes, the heart and brain, and kidneys are very important for the individual. The reproductive system is important for the species to continue to exist. And so, that was one of the reasons why I chose to do what I do. So, yes, I do all of these things. My

bread and butter is obviously that I trained to become an OB-GYN doctor and then subspecialized to be a reproductive doctor and treat infertility.

But there's a very specific niche or a really specific field within the subspecialty of reproductive medicine that I'm very passionate about, and that is fertility preservation for patients who have medical conditions that mandate fertility preservation. And when we talk about those, the vast majority will be patients who are facing a cancer diagnosis. There are also other medical conditions, treatment of wedge can lead to diminishing future fertility, and so we encompass them as well. And if everybody's okay with that, I'm going to share, I have several slides, I mean not several, maybe like 20 slides or so to share, but I'm going to share a screen and please let me know if everything... Looks kosher. Okay, hold on just a second. I actually need to stop it and do it from the beginning. I'm so sorry about that. Just one little second. I apologize.

I guess we do need to put this on the beginner slide and then share it that way. So let's do this. Meanwhile, I do lead our team in the Brooklyn Center, which is located in the heart of Downtown Brooklyn, and this is a new IVF lab that we opened about a year ago because several things that have happened in the past two years, what the pandemic have really driven the need in the most populous borough of New York City to have access to care in their borrow in their backyard. Well, there's a good reason and a bad reason. The good reason was that we became a mandated state and we're so proud of it. And I'll talk about it a little bit obviously during my presentation as well. We became a mandated state in early 2020 for coverage for infertility treatments, but we also became a mandated state for coverage for patients who need to preserve their fertility in the setting of a medical condition, the treatment of which we know can result in diminishing of their fertility.

So cancer, the BRCA gene, certain genetic mutations that we know can result in needing surgeries and needing treatments that will tarnish future fertility and so forth. And then the second thing is that most people stopped really going to Manhattan to work and just stayed in Brooklyn, where they live and work, and worked from home. And so there was this amazing need that needed to be filled. And so we opened a center, but I'm here really to represent Mount Sinai and RMA of New York. Those are the two organizations that are married together. RMA of New York has been in existence for over 20 years now, and we are the reproductive division of the OBGYN Department of Mount Sinai.

And I wanted to talk to you about fertility preservation for patients who are undergoing or who are facing a risk of their fertility being diminished by their medical condition or the treatment of that medical condition. So I have no conflicts of interest. And the biggest question is really like why do we talk about fertility preservation? And as Alona mentioned, I mean, this was 10 years ago and I'll present some data that even 10 years ago this was really recommended and there were strong recommendations to discuss this with patients. But alas, we were not at that point yet. The reason for discussing fertility preservation is that even though some approximately, what is it about, maybe 10% of the cancers are diagnosed in people of reproductive age as opposed to a vast majority being diagnosed in people who are past reproductive age in at least in our parameters, that's about 9% or 10% or so.

The vast majority of these people actually survive. And survival is, at this point, over 85%. So people who are diagnosed with cancer, any type of cancer within the reproductive years, not because of reproductive years, but because these are young, healthy people and it's so coincides, but also being of reproductive health are young, strong, they have good hearts, good kidneys, and they have very, very good chances of surviving cancer, surviving the treatments, being strong enough to go through the treatment and to actually live after as opposed to some 67% of people overall especially. And that number goes down if you think about people who are older than 45 or 50. The majority of these cancers are going to be in specifically people with ovaries or women of reproductive age or breast cervical,

leukemia, melanoma, and Hodgkin's lymphoma. Those are the most commonly diagnosed cancers in this age group.

There are major health conditions that are diagnosed in cancer survivors or post-vivors as we call them. And ovarian failure is one of them that is seen dependent and it's very dependent on the age at the diagnosis, on the dose of the medication, type of medication, type of cancer and so forth, as we're going to elaborate in the next few slides. The cumulative incidence of a chronic health condition within 20 or 30 years after the cancer treatment is about 70% for cancer post-vivors and cumulative incidence of severe disabling or life-threatening conditions is about 40%. Risk of premature ovarian insufficiency is also increased as we know in patients who are diagnosed with these conditions if we need specific treatments, because it has been discovered, and we know this for about 30 years now, that certain treatments, specifically certain chemotherapeutic approaches as well as certain radiation therapy treatments are associated with the higher risk than others.

But it also depends on the age of which you're diagnosed with the disease because ultimately it has to do with the number of eggs that are left. So a certain chemotherapeutic regimen or certain radiotherapeutic regimen will always be associated with just killing a very set number of eggs, and it really will depend on how many eggs you have at that point. So let's say you have 300,000 eggs at that point, and we know that this chemo will destroy 100,000, sure. If you're 300,000 and chemo will kill 100,000, you'll be still left with 200,000 and you'll be fine. You might go and menopause a little bit earlier, but you are still left with a good number. But let's say you're 42 and you have 70,000 left and you get chemo that kills 100,000, we almost certainly expect that premature ovarian failure or insufficiency will happen.

Specifically, when we talk about our community, well, not all of our community but the people of Ashkenazi descent, we are more likely to be carriers for certain genes. That's what it comes with the territory. So while the risk of BRCA mutation is found, one in 200 in the general population for people of Ashkenazi descent, the initial data several years ago was showing that it is found in one in 50. Newer data is showing that it's one in 47 and the two most common mutations, even though nowadays we really sequence the whole gene, part of BRCA1 and BRCA2, these genes are involved in repair of DNA damages and we know that there are slightly different risks of certain cancers, but they also exist with both mutations. BRCA2 seems to be a little bit better than BRCA1, but both are associated with development of cancer at some point in life, specifically breast cancer for both males and females, pancreatic cancer, ovarian cancer, prostate cancer, but also melanomas and several other things, even some uterine cancer and GI cancers.

So this is one of the studies, and I'm not trying to get too scientific on you, but one of the largest studies that looked into the fertility potential of people who have been diagnosed with cancer before the age of 20 and compared that fertility potential to their siblings who have not been diagnosed with cancer and encompassed over 5,000 people in the study that show that there's a relative risk of having lower chance of pregnancy specifically with certain types of radiation. If it's related to the hypothalamus with pituitary gland such as some intracranial cancers or obviously radiation to the ovaries or the uterus, there's a higher risk of infertility even in people who have received SAP clinical doses that would not put somebody into menopause right away. And of course the highest risk of premature menopause as we now call premature ovarian insufficiency is seen in inpatients who have been diagnosed with cancers that would require cyclophosphamide.

That's a bad one. Running of the alkylating agents for people who need total body radiation in preparation for bone marrow transplant. So having that leukemia or lymphoma that is not responsive to the first or second line treatment which needs total body radiation, those are the treatments that have the highest potential to just bring a person, regardless of age into premature menopause. But as we

said, it depends on the type of cancer and the age of which you're diagnosed. There are definitely some genetic differences because, just like when we talk about fertility, there are people who get pregnant at 42 like this and there are people who are starting to slow down and need some help in their mid-30s or late 30s. We also do see some differences when it comes to the response to chemotherapy and radiation.

There are several mechanisms and what's really interesting is that most people think that the mechanism is like, okay, the chemo just destroys everything, destroys the eggs, and that's it. But it's been found in many different chemotherapeutic agents and as well as radiotherapy is that the way that the ovaries formed during embryonic life is because the ovary, unlike the testicles, is a non-regenerative organ and we do not create new eggs upon earth. There was some data that came out of Harvard over 20 years ago, they were never corroborated and was actually refuted by other respected institutions. We don't believe there is any new creation of new eggs or regeneration of eggs upon birth. Testicle, on the other side, contains stem cells. And so boys, when they enter puberty start to regenerate or to differentiate these stem cells into sperm cells every two months. That's why Trump can conceive Barron at 68. Maybe needed some help, but it's possible. For us, it is not possible and there is a common way of a lot of chemotherapeutic agents will be just destroying the actual eggs or the actual cells that are contained within the follicles.

But a lot of the other ones that are... And how chemotherapy or radiation is differentiating cancer tissue from your healthy normal tissues is by the number of divisions by the metabolic activity. I mean, the cancer tissues tend to have more metabolic activity there just overgrowing, they're going crazy and this is what a lot of chemotherapy or radiation is going to be aimed to do and they don't kill you while killing the cancer. So those are some of the mechanisms how they work. Cyclophosphamide, for instance, that is used and it's a very good chemotherapeutic drug, that's why it's used in so many different protocols including treatment for breast cancer and colon cancer and ovarian cancer and so forth, it's actually not specific and it does not just detect the cells that are in a certain phase of metabolic activity or division, but they just kill everything. The good chemotherapeutic agent, unfortunately that is why it is one of the most dangerous ones that we talk about, the damage of the reproductive system for both men and women.

We also know that there are certain doses of the radiation therapy afterwards, there's just like there's nothing there. And so, it really depends on what is needed, but also location. Let's say you need a radiation of the brain because there's a brain tumor or pituitary tumor, you might not have the activity of the pituitary that is needed to activate the ovaries and we need to help you a little bit by stimulating the ovaries, but the biggest concern for us is when those eggs or those sperm cells are actually effective because we cannot replenish those.

Even the uterus, believe it or not, is a target of this damage by some of these treatments because there is a very specific layer of the uterus and if you think about it, it makes sense. Uterus itself is a bag made out of muscle, but there's a lining of the uterus and the base layer of that lining is what we call stratum basales, and that one is the one that contains the stem cells. And every month from that very thin layer to extra layers develop as a consequence of estrogen from the growing follicle from the egg that is about to ovulate and be released. And if you don't get pregnant that month, if you're not trying to get pregnant that month, those two extra layers will just be shed in form of your period. So that is what the period is, that stratum basales or that basal layer that contains the stem cells always need to stay and needs to stay protected and to survive.

And because stem cells do have higher activity, metabolically speaking, than cells that are not stem cells, the uterus can also be a target of some of these chemotherapeutic agents as well as radiation. So in some patients, we do see that if they receive palliative radiation specifically for cervical cancer or some

types of uterine cancer even that precious layer that contains the stem cells will not function anymore and there won't be development of the endometrium or that lining.

Risks really if you want to look at it grossly and how we generally stratify the risks for patients is really based on, as we said, the age as the chemo will always destroy a certain number of cells, and so it really will depend on how many cells or how many eggs you have at that point in time. So being older or not having that many cells left or needing total body radiation, need a really high dose of cyclophosphamide or alkylating agents that we said will destroy cells and will not spare the ones that are not active but will just kill everything that gives a very high risk.

And then there's intermediate risk with being a little bit younger, needing a lower cumulative dose. Lower risk is seen luckily with a lot of the treatments that are used as a first-line treatment for leukemia or non-Hodgkin's or Hodgkin's lymphoma, which are commonly diagnosed in the population of women who are reproductive competent. So oftentimes these patients actually will be very sick at the time of diagnosis and oftentimes will not have time to preserve fertility, but we actually don't really worry about them that much because the first-line treatments are not that toxic at all. And then there are some that have very low risk or no risk or maybe not no risk at all, such as 5-FU, which is used to treat some skin cancers, methotrexate, which is used to treat even ectopic pregnancy or certain rare cancers, and so forth.

So why I always bring up the slide, it comes really back to what Alona was saying is that since 2013, American Society of Clinical Oncology has been highly recommending that every patient of reproductive age who has been diagnosed with cancer should see a reproductive doctor and have a conversation, or if that is not an option, have a conversation with their treating oncologist or surgeon or radiation oncologist about the potential of the treatment that they're about to receive that can diminish their fertility. And that has been the recommendation for about 10 years now and they keep renewing it and it keeps getting reinforced. Unfortunately, in reality, only approximately 50% of cancer patients of reproductive age are actually being referred to a reproductive specialist and probably less than 30% of those patients who are being referred are actually being seen and are undergoing fertility preservation.

And there are many different barriers to it. Obviously some barriers are going to be related to the patient, if the patient does not have a good prognosis, if a patient is really, really sick and we're really fighting for their life, this is extra, this is luxury, in that case, and we're not really thinking, unfortunately, about the life after the cancer or if being a female is definitely a risk factor because, I mean, we have patients who's sperm has been sent to us posthumously, meaning they have died already, sperm was collected after they have passed and frozen.

For women, the process takes much longer, it's more complicated than just masturbating into a cup of sperm. And so by virtue of the complexity of the process being of a female sex or gender is less likely. Is it risk factor for not being referred? Also, extremes of reproductive age. I mean, we could theoretically stimulate a baby who's two years old, the whole access is formed and you could actually perform control ovarian stimulation, retrieve the eggs, but it's not considered ethical to activate the reproductive access that consists of the pituitary gland, higher centres in the brain and the ovaries before its time and it's time for activation is when they go into puberty.

So we don't really resort to fertility preservation other than just ovarian tissue preservation during surgery in people who are pre-pubertal. There are definitely some providers that are better than others. Obviously providers who are dealing with treating female patients, which would be breast cancer surgeons or breast cancer doctors or GYN oncologists are better than people who are treating the conditions or just have less knowledge. I mean, I'm talking about this for four years now that I've been at Sinai at meetings for radiation oncologist and GYN oncologist and med oncologist, surgical oncologist, and it's still, it's a work in progress. A lot of people still do have this notion that, "Oh my god, it's cancer.

There's no time, this patient needs to survive," and everything else is not a given, but again, we know that the majority of people diagnosed with cancer at an early age, which is younger than 45 or 50 will survive that cancer, we know that from the data in the past 30 years.

And so, we really need to focus on the quality of life after that cancer and not just worry about, "Well, was the patient going to survive?" That is a very rare scenario. Obviously, it happens all the time and it's really sad when it does, but it's a very small proportion of people who are diagnosed with cancer at a younger age who don't have a good chance of surviving. And then resources and a lack of referral process, which is something that we are working on and we were able to overcome at Sinai.

As I said, we're very lucky in the state of New York that for patients who were diagnosed with cancer as well as other medical conditions, treatment that has the potential to tarnish or to completely diminish their future fertility, there is coverage. It is still not going to be at a federal level, it will never be at a federal level, but at least major commercial insurance companies are covering this. And so we are lucky, but we're only the eighth state in the country that has this privilege.

There are several different options to preserve fertility. As we said, and I will take you quickly through the process of egg freezing and that will probably I'm going to be wrapping up my talk here, but there are several different things and there are things such as fertility-sparing surgery and embryo cryopreservation and oocyte cryopreservation using Lupron as Alona said, and we'll talk about that in a second as well, to try to suppress the eggs and put the follicles in a state of less metabolic activity because as we said, a lot of chemotherapeutic agents or radiation therapy as distinguishing cancer tissue from healthy tissue based on the level of metabolic activity.

So if you put the eggs or the follicles into a state of lower metabolic activity, the idea is, oh, well, maybe you can preserve them that way. Transposition of the ovaries or oophoropexy if there's a radiation need in the pelvic and then ovarian tissue cryopreservation. So transposition is pretty simple and really used in very limited situations when patients do need radiation in the cervical pelvic area, you can put the ovaries up. It's a very simple surgical procedure where we basically remove the ovaries out of the pelvis. We don't detach them from the uterus, we just suture them to the abdomen so that if the radiation is really focused on the cervix or vagina for cervical vaginal cancers, rectal cancer the ovaries are going to be outside of the radiation field.

Now, this is really important and this is what I talk about every day, multiple times a day. This is basically what egg freezing entails and this is the process that is exhaustive, and it is not pleasant, but again, I offer it 20 times a week for no medical reasons to women or people with ovaries who wish to just preserve their eggs because they are not ready to have a family completely electively. So on the other hand, it is not something that is highly risky and we'll talk about it in the setting of estrogen sensitive cancers. But basically what I like to explain when I talk about the control ovarian stimulation is, it really brings us back to how the ovary functions, how the ovary is formed during embryonic life and what happens every month during a normal menstrual cycle. So we're born with a finite number of eggs, and as we said, the ovary does not regenerate eggs unlike the testicle that regenerates from cells starting in puberty until the man dies.

There's a little hack that nature has thought of, which is to basically contain each egg within a structural follicle at birth. So this is how the ovary is organized. It contains all these eggs, about 1 million or 2 million at birth in a female neonate, but each egg needs to be contained within the structural follicle, which basically comprises a group of ovarian cells that are protecting the egg and keeping the egg at a state of no metabolic activity. And if you will, all these eggs, a majority of them at any point in life, even at the time of menopause, are going to be in a state of no metabolic activity. So imagine your eggs are basically frozen inside your ovaries, that's basically what it is. And so, once we hit puberty, we have about a quarter million eggs left, down from 1 million or 2 million.

Nobody knows why a baby would need 2 million eggs if it's not even reproductively competent. And once you reach reproductive competency, we had about meds fund, you're supposed to start procreating at 13. We don't do that anymore. The life is different nowadays, but that is really when biologically speaking, we are at the peak of our fertility. What starts happening is that from that frozen pool, imagine there's 249,990 frozen little eggs in little follicles that are microscopic here in this area of the ovary. And then 10 follicles, well, something activates them, they start developing and they develop over a course of couple of weeks and they reach the size of four to eight millimeters, they reach developmental stage that we call antral follicle and we can actually see these with our naked eye or by the ultrasound.

And so what happens and what's really interesting is that our pituitary gland, which is a little gland in our brain through production of two hormones, one is called FSH, the other one's called LH, is then selecting one queen bee of these follicles, only one to be the dominant follicle, and that one grows bigger and faster than the other ones and in about two weeks or so, that one will mature the egg, erupt to release the egg. It's fascinating that if you look at the laws of Halacha and so forth, you're supposed to go to the mikveh around day 12 and that really puts you into the peak of your fertility because that is around the time when you should be maturing this egg and releasing this egg. If you have a 20 day cycle, you ovulate around day 13 or 14.

All the other ones, let's say 10 other ones that developed in the same cycle, they will die. That's a difference between mono-follicular species such as us, primates, cows or sheep and polyfollicular species such as mice or cats, that's where they have litters. If the size of this cohort that develops every month is 10 follicles, that won't maybe use seven out of it and have seven pups, we only have one.

So when we go through controlled ovarian stimulation to gain access to the eggs to freeze them specifically in the setting of patients facing a diagnosis that we know will lead to the loss of these eggs, we want to change the ratio at the level of that cohort and try to mature. If the cohort is 15 follicles, instead of one growing and 14 dying, we want to have 13 or 14 growing and one dying. And that's basically all there is. And it's based on the same principle that happens in a normal menstrual cycle, which is used slightly higher doses of those hormones that pituitary gland normally produces FSH and LH, we use it in a slightly higher concentration so that we change the ratio. Unfortunately without freezing the ovarian tissue, we cannot get into the little guys that are frozen here. And so, the stimulation lasts for about seven to 10 days.

Once follicles reach a certain size, we perform the minimally invasive procedural egg retrieval that is done under sedation. It's not painful, it takes about two or three minutes. It's very quick and the needle that is used is basically traversed through a little tunnel on the ultrasound probe. So it's guided by the ultrasound, it's very safe and the thickness of the needle is about the same as the thickness of the needle that is used to draw her blood. They suction the fluid and the eggs from follicles on both sides, then we freeze the eggs. And if a person needs to use these eggs in the future, we can make them into embryos and take it further. Or for couples, I have many couples who are facing, a couple who has a child already or a couple or a woman is diagnosed with cancer, then they will just proceed with freezing the embryos and once it's safe to get pregnant, they will be able to use these embryos.

There are a few protocols that have been established because a lot of people will always ask, especially in the setting of an estrogen sensitive cancer such as uterine cancer, breast cancer, more or less ovarian cancer, but not so much, some types of melanomas. If you're maturing multiple follicles and multiple eggs, that does proportionally increase the amount of estrogen that is produced from these follicles and it's proportional to the number of follicles that are growing and normal menstrual cycle when there's only one follicle growing, only one egg being released, estrogen should not exceed 250 to 300 per ml. But if you have 10 of them growing, it might be about 3,000 or so. And so for patients who are

diagnosed with estrogen sensitive malignancies, we do recommend using certain additions or additional medications to the protocol which includes tamoxifen that is also used in prophylaxis.

Nowadays it's really letrozole because it just diminishes the amount of estrogen produced more efficiently than tamoxifen so that the stimulation is such that it does not really exceed the amount of estrogen produced in a normal menstrual cycle even though we have multiple or multi-follicular development. The safety has been compared in one or two studies and it showed no increased risk of recurrence in between patients who have never gone through fertility preservation using letrozole and patients who have. We also use an approach that is a little bit different in what we do, we do bread and butter IVF for egg freezing and that is that we just start whenever like I see a cancer patient, so on today and we soldered the patient this evening. Typically, in the IVR process, you would see a patient, let's say, a woman is going through fertility treatment or egg freezing electively or we call it as part of preventative measures, a single 34-year-old woman who wants to have kids in the future.

Ideally, you want to start the simulation by day two or three of the cycle, before her brain has selected that one dominant follicle that we said will grow bigger and better than the other ones and the other ones are destined to die. But in patients with cancer, there's no time. You can not just wait for two weeks for her to reach that point if she just saw you a day after ovulation, because in two weeks, she's already scheduled to start chemo. And so we have studied this and this is the study extensively and we know that there are pretty much only two points in the cycle when we want to wait for a few days and that is right before ovulation or right after ovulation. Otherwise, any time or random start stimulation is as good as a traditional day two start.

In fact, we're using this more and more in patients who are not freezing eggs or going through stimulation for cancer reasons only, but we're extrapolating this data that we know from cancer patients to many other different patient and groups. We know that the simulation might be a day longer and you might need a little bit more medication, might be one day longer.

Speaking of what Alona mentioned earlier, even though there have been so many studies looking into and really good and well designed studies, prospective randomized controlled trials, and that is the highest level of evidence in medicine and in humans. Randomizing people to receive Lupron or one of the GnRH agonists to suppress ovarian function as we said, so that you keep the metabolic activity of the ovarian follicles or ovarian activity to the minimum so that there are less of a target for chemotherapy or radiotherapy that we know is targeting cancer tissue and differentiating it from your healthy tissues by the level of metabolic activity. More and more data, and when you pull all these studies together, it's showing that that might not be that much of a benefit.

I think it really depends on which chemotherapy you're using, what's the age of the patient and if you're using an agent that is targeting cells, regardless of whether they're metabolically active or not, we still recommend it based on the recommendations from really this year, last year, we're still recommending to patients to receive it, but it might not work especially if you're getting a cyclophosphamide or so.

And just a few slides on ovarian tissue transplantation or cryopreservation. This is really the only option for children for pre-pubertal children who are diagnosed with cancer. And we see a lot of these unfortunate patients as well. They have an excellent prognosis, most of them, and they will survive the cancer treatment, but the ovaries will get damaged to the point that they will not even go through puberty, let alone have fertility in the future. As we said, we cannot really stimulate a two year old baby and retrieve her eggs and freeze them. So we resort to freezing the tissue and then once the ovarian tissue is frozen, it can be transplanted back into the body once the person is completed what their treatment, it can be transplanted back onto the ovary. We usually remove one ovary and leave the other one in the body and then we transplant tissue of the one that we froze onto the ovary that we

kept in the body or we can transmit it into an arm or into other part of the body where it can be easily retrieved.

In fact, the first case that was published at this point 21 years ago by one of my mentors and colleagues was transportation into an arm and they were able to stimulate follicles from there. At this point, this is a little bit outdated because not everybody's really pulling their data into the database, but ovarian tissue preservation is no longer considered experimental because there's probably over 200 babies born through this method. And so, it can also be used in patients, not just pre-pubertal children, but in patients who are too sick to undergo egg freezing or embryo freezing and need therapy that we know will be very good but toxic and therefore the surgery can always be performed and the tissue can be frozen. We have a really big team at RMA and I think that we're really trying to break some of the barriers that exist for people getting access to care through altruism, through several grants that we work with, some internal and some state grants and some private grants, and also being blessed to practice in a state that has provided access to care and is covering fertility preservation.

In this setting, there are over 20 people on my team, there are five doctors, including myself. So we at Sinai commit to seeing a patient within 48 hours of when the request is made. And because these patients, this is our emergency, I know it might be laughable for some people who are surgeons who are like, when we talk about life and death, but for us this is an emergency and we take this. This is the most serious thing really that we see in our field. So that's it. This is our team. We're a big team, I think 19 physicians at this point. We have three fellows and 26 residents across Sinai and a lot of medical students. And that's really what I have for you. I'm really open to some questions. Sorry, I've been talking for so long and I wish these are happening in-person as they used to because I do think that we lost some of the personal touch and ability to connect as humans, but I think at this point, we're all very accustomed to Zoom and to virtual world. So that's all I have for you.

Eve Kleinerman:

Great. Thank you so much, Dr. Lekovich. Thank you for educating us all on such an important topic. And I know your presentation answered so many of my questions and I'm sure it did the same for everybody. We do have several questions that came in. I just want to let everybody know, if we didn't get to your specific question, we'll try to answer the questions tonight that are a little bit general if possible. And if you don't see an answer to your question, you can reach out afterwards as well. As we are running a little bit short on time, if you do need to sign off, our recording will be available online, but I'm going to see if Dr. Lekovich can answer one or two questions here this evening. One question is for somebody who had chemotherapy and other treatments, and their period has not returned and so they're trying to promote ovulation, consider fertility. Are there any suggestions that you have on prompting that along?

Dr. Jovana Lekovich:

So this is a very important question and I think it's really important to understand. It comes down to what we talked about like how the ovary is formed. If you remember at any point, 99% of the eggs will be in that state of no metabolic activity, they're basically frozen. And unless you're receiving chemotherapy or radiation that is really going to target those that are not metabolically active, the ones that are going to get destroyed is just like the tip of the iceberg and the majority will be preserved. But sometimes for those that are metabolically inactive, you might take a couple of weeks, couple of months, even up to a year to get activated and to position themselves again on the surface of the ovaries. So I think it's really important in what I do with my patients who have gone through the treatment is I follow them and once they have completed chemo, we have follow-ups every three to four months.

For a full year, I follow the parameters of a variant reserve. We do an ultrasound looking for something called antra follicle count, which is where we look to see if we can see any of those follicles positioning themselves on the surface. We test hormone called AMH or anti-mullerian hormone and we test hormones that ovaries should be producing and which follicles are active and which are estrogen, progesterone, and then we check some pituitary hormones as well.

Even if let's say it's been a year and there's no period and there's no appearance of the follicles and all the parameters are appearing to be at zero, there's still a pretty good chance of one little follicle being left out there and just developing one day and just ovulating. And the problem is you won't know. So if you're somebody who's trying to conceive and you've been diagnosed with premature insufficiency after a year of no activity being sent in the ovary, the best idea honestly, and the best thing to do is to either see a reproductive doctor or gynecologist every two or three weeks to see if there isn't any activity or if you have a male partner to be intimate two or three times a week throughout your life, that way you're not going to miss it and you still have a good chance of getting pregnant.

Eve Kleinerman:

That's great. And then very quickly as the last question here, I'm going to combine a concept that many women have asked, which is that if one has gone through treatment for cancer, in this case, breast or ovarian cancer, is it considered to be safe to go through this type of hormone-stimulating treatment? So let's say doing IVF or doing an egg retrieval post-cancer treatment.

Dr. Jovana Lekovich:

So that is something that we always discuss with the treatment doctor with an oncologist or radiation oncologist or a breast surgeon or duo oncologist, that's the primary doctor because there's not all ovarian or breast cancers are created equal and it really depends on the stage and the type of the cancer receptor status, grading of the diagnosis, what treatment the patient has received. But yes, it is possible, I have patients who have DCIS or ductal carcinoma in situ who were just treated with surgery and receptor status was adequate and their ovarian result was not diminished by the treatment or was diminished, but usually they just needed a surgery, they were allowed to go through the treatment. We always would use letrozole or Femara, which is an aromatase inhibitor, it's a medication that is used very much as part of the prophylactic medication after estrogen receptor-positive treatment.

We use the same medication to keep the estradiol levels low through the stimulation, but absolutely, ultimately it really depends. There's no unique answer to that and we always work with the team. And really if there are any more questions, I'm really open, please refer any emails to me or you can contact me through Instagram or any other means of social media. I'm happy to answer to the best of my ability and my knowledge because I'm sure there are many questions that we left unanswered because this is a limited time that we had.

Eve Kleinerman:

Yes, thank you. Thank you so much, Dr. Lekovich. Thank you for educating us this evening, for answering the questions and for your generous offer to continue with questions afterwards. We have had a great evening of education on hormone therapy and usage and I know that we all feel more knowledgeable after hearing your presentation. I also again want to thank our sponsor for this evening, which was Merck. And it's thanks to Merck that we were able to have a two-part hormone series. As you can see in the chat box right now, a brief evaluation survey link is there, if you can please click on that now, you'll still be able to hear the last few announcements. Your evaluation response is really due in a form for our

future programming. The other link in the chat box is a link to Sharsheret's fertility resource, which is also relevant to so many of us this evening.

And please do check out our Sharsheret website regularly. We have a busy summer with exciting events. We have a lot going on both in-person and virtually. And you can see all of our upcoming events as well as access the recordings and transcripts of all of our past webinars on our website. And please never forget that Sharsheret is here for you and your loved ones during this time. Sharsheret provides emotional support, mental health counseling, and other programs that are designed to help navigate you through the cancer experience. All of our programs are free and completely private, they're one-on-one and our content information is in the chat box now as well. Our social workers and genetic counselor are available to each and every one of you. You are all of our priorities, so please never hesitate to reach out. Thank you so much and have a great night.

Dr. Jovana Lekovich:

Thank you. Thank you. Thank you Sharsheret for everything that you do and for inviting me. And again, if I can be of any future help, please let know. I'm available 24/7.

Eve Kleinerman:

Thank you, Dr. Lekovich. Good night.

Dr. Jovana Lekovich:

Bye guys. Have a good night.