Melissa Rosen:

We are so glad that you are here with us this evening. This is actually the first in a two-part series planned for young women. Today we will be addressing medical menopause and fertility preservation. Next month we will exploring the impact cancer has on intimate relationships and sexual health. Of course, I want to be clear that anyone is welcome to participate in this series of webinars and that young is very loosely defined.

I want to begin by thanking the sponsors of this series, Daiichi Sankyo, Pfizer, and the Cooperative Agreement 19-1906 from the Center for Disease Control and Prevention. Their support allows Sharsheret to continue to offer meaningful programs such as these. As always, this program is being recorded. Yes, I just double-checked it is being recorded. No faces or names will show in the recording other than those of the presenters, but if you wish to turn your video off, for privacy you can absolutely do that now. The option to do that is on the bottom left of your screen.

You can also choose to rename yourself if you prefer to remain anonymous. You can do that by clicking the top three dots on the right hand of your photo square. And directions to do that are in the chat box now. To participate anonymously simply so let's stop video and rename yourself. We also now have closed captionings available. Instructions on how to access them are in the chat box.

Begin the Q&A at the end of the presentations with the many, many questions that were asked as part of the registration process. Of course, I want to remind you, you are still able to ask any questions that may arise during the presentations. Please place those questions in the chat box and we will be monitoring it. To send a question or a comment anonymously in the chat box, please click on the button that says everyone, and then simply select Melissa Rosen, Sharsheret. And it will only be visible to me. Okay, let's dive in now.

We know that cancer is about so much more than the actual cancer itself. When someone is diagnosed with cancer or is concerned about a cancer diagnosis, so many related concerns arise that affect us emotionally, that affect us physically. And those are some of the things we're going to talk about today. But before our experts begin, we are fortunate tonight to have a Sharsheret caller named Alona with us. She's joining us to share her experience with medical menopause and fertility preservation. Alona, I'm going to spotlight you and thank you so much for being here this evening.

Alona Shaked:

Yeah, thank you so much for having me. I really appreciate being here. And I'm just going to go ahead and tell my story. And then of course, if there are any questions, I'm not sure that I'll be able to stay on until the Q&A, but if anyone has questions for me, you can get my info from Sharsheret, or you can follow me on Instagram or something. Okay.

So my name is Alona Shaked. I was diagnosed suddenly with breast cancer when I was 28. I found a lump in my left armpit area while I was massaging myself after a difficult workout, I thought I felt something, went into the doctor's office and a few days later I got a call while I was at work telling me that I had breast cancer. And obviously at age 28, that was a huge shock for me. Cancer was not on my radar. Motherhood also was not on my radar at that point. I was working as a lawyer at the time. I was very career-focused. I just took everything for granted thinking that I would have kids sometime in my thirties.

And in the very beginning of the diagnosis, it just seemed like things were getting worse and worse. Every day I got more bad news. First it was the cancer was aggressive. I had more than one tumor. I had the BRCA1 gene mutation, which I'm sure many people who are part of Sharsheret know what that is or have some type of genetic mutation. I learned that I would lose my hair from chemo and that I could die from full experience of course. But I think one of the hardest things for me and most surprising pieces of information that I received were that I might become infertile because of the chemotherapy that I was undergoing. Again, really this was not on my radar. Motherhood was something I planned to do in the

future, and then all of a sudden it was like one of the most important things to me. One of my biggest concerns.

So I was diagnosed 11 year, almost 12 years ago, but 11 years ago. And at that time, fertility preservation was still not the standard of care. So I was not offered fertility preservation as part of my treatment. I did my own research and I asked about it and after a long conversation with my oncologist of the pros and cons, we decided to move forward with one cycle of egg freezing. I did that one cycle. I had very, very disappointing results. I only managed to get two mature eggs, which if anyone here has undergone fertility preservation for somebody who's 28 to only get two eggs. Each of those eggs, I was told, had about a 5% chance at best of becoming a baby. And so that was super disappointing at the time. I'm going to get back to that though.

At the time, my doctor also offered me an experimental drug called Lupron, which was experimental for the purpose of fertility preservation at the time. They were using it for estrogen suppression but not for fertility preservation yet. And so we actually had to code it for my insurance company as a hormonal therapy rather than as fertility preservation. That shut down my ovaries for the duration of while I was under treatment. So I was in medical or chemical menopause during that time.

It's very hard for me to say what part of my intense brain fog and utter feelings of just not feeling my best were due to the menopause and what was due to the chemo or the stress of dealing with cancer. But suffice it to say all of those side effects were things that I was experiencing. Felt like there was a cotton ball wrapped around my brain for a year. And actually, to be honest, I was really never quite the same after that even though my period did come back after I finished chemo and after I stopped taking the Lupron, I have been perimenopausal. Also, nobody tells you that having a period doesn't necessarily mean that you're fertile.

So fast-forward through six rounds of chemo, double mastectomy, the reconstruction, the whole deal, and I am now 35 years old and I'm getting married. And I figure, "Okay, great. My period's back. We're just going to start trying. It's going to happen." After a couple of months, it became evident that things were not going to move along that quickly so I decided to make an appointment with a fertility specialist knowing that I had some challenges with that first egg retrieval. And I went through seven more egg retrievals in order to be able to get a viable embryo. I went through multiple failed transfers, and finally I got pregnant in February 2021 and my first daughter, Ella, is now two and a half years old. So that was an incredible miracle, a great success.

And then of course, we decided we wanted to have a second child. So there I was then at that point already 38 years old. And so knowing what we knew about my egg quality and chances, we decided to go straight back into IVF. We had two embryos leftover from the extra IVF we did, and then we had those two eggs that had been frozen for 11 years. I went through two more failed transfers, including a chemical pregnancy, and finally again, got pregnant. One of those two eggs that I froze all those years ago is now my daughter Sophie, who is three months old.

So what I want to say is first of all, miracles really do happen, especially when you have the science to back them up. Even in very, very difficult situations, I think there's always hope for creating a family. And it was a hard, very long, difficult journey, but I learned a lot through it. And here I am today. So I'm now 40, it's been almost 12 years, and I have BRCA1. So as some of you may know, that means it's well pastime for me to start removing my ovaries, and that means surgical menopause. I think that for me, the biggest barrier to deciding to have the surgery has been, number one, I wanted to make sure I finished having my kids. And then number two, I'm really not looking forward to being in menopause earlier than I'm supposed to be.

Obviously it's a big conversation that one has to have with their doctor, with their oncologist, with your gynecologist, with whoever your work. I don't see an oncologist anymore actually. But I will actually be doing HRT, which was a very long discussion of pros and cons and a lot of research and a lot of soul-searching. But with that in my back pocket, I'm hoping to do my surgery this fall. And while I can say I'm

really sad about going into menopause finally, again I experienced it while I was in chemo, but who's to say how much of that was actually the menopause versus the chemo? While I am sad about that, again, when I think about would I trade this for my life, the answer is always no. And I want to be here for my kids growing up now.

So that is my story. And again, if anyone has any questions or wants to get in touch with me, you can contact me through Sharsheret or you can find me on Instagram. My Instagram is alonagabrielle and I post a lot there about my fertility journey and my experience. So if anyone is going through something similar and just needs to see a success story or talk about it or anything like that just to connect, I am there for that. And I wish everyone here the absolute best of luck on your personal journey. It is not an easy journey, but it can be very rewarding sometimes.

Melissa Rosen:

Thank you so much for being so open with us and sharing your story. I know that it resonated with so many people on the screen, so thank you. Oops. I'm going to remove the spotlight so you can listen to the rest or go to bedtime or whatever you need to do.

I wanted to introduce our first doctor presenter tonight. Our first doctor this evening is Dr. Elisa Krill-Jackson, who will discuss the many aspects of medical menopause as it relates to the cancer experience. Dr. Krill is a board certified hematologist and oncologist at the UHealth Sylvester Comprehensive Cancer Center in Miami, Florida. She specializes in breast cancer and gynecologic cancers, as well as hematology. Dr. Krill believes in educating her patients about their conditions so they can work together as a team in fighting their cancer. While using the most state-of-the-art treatments and clinical trials, she believes in treating the whole patient with compassion and supporting her patient's physical and emotional needs. Thank you so much, oh, for being here.

Dr. Elisa Krill-Jackson:

Thank you for having me. Oh, I'm very blurry on the screen. My lighting is bad.

Melissa Rosen:

But we hear you nice and clearly.

Dr. Elisa Krill-Jackson:

It really is bad. I don't understand. Anyhow, that sounds like something I wrote for a website.

All right, I'm going to talk about medical menopause. And I think Alona did a really nice job talking about her journey. And we see this all the time in our patients. It really is hard as a young woman to undergo menopause that early, but menopause is a fact of life pretty much for everybody as they get older. And there are ways to mitigate symptoms, and I think in general we're fairly successful in mitigating the hardest symptoms and making things more tolerable. So I'm going to share my screen and we can get going. Can everybody see my slides?

Melissa Rosen:

Yes.

Dr. Elisa Krill-Jackson:

Okay, terrific. All right, so let's talk about medical induced menopause as it relates to breast cancer. Oh goodness. How do I forward my slides? There we go. All right.

So first what I want to do is I want to talk about... Sorry. A little glitch while I get rid of everybody's faces so I can see my slides. I want to talk about estrogen production and how the body produces it because I think that's very helpful for patients to understand. So how a normal pituitary and ovarian function works is that you have a gland in your brain called the hypothalamus, which secretes a chemical called GnRH in a pulsatile manner. So in a pulsatile manner, it stimulates the production in the pituitary of two hormones called LH and FSH, which stimulate the ovary. And they stimulate the ovary to produce estrogen and to ovulate.

Normally when somebody ages, menopause happens gradually. People's estrogen levels fluctuate. They go a little up, they go a little down. They may have symptoms that get better and worse over time and eventually their periods will stop. But the ovary actually probably still makes a slight bit of estrogen after period stop over time. This is different than egg production. So there's two parts of the ovary. The first part makes eggs, the other part makes estrogen, and you can damage the egg production while still having the estrogen production.

So how do we stop your periods? We can give something called GnRH analogs. The most common ones we used are called Lupron and Zoladex. That is a big large GnRH signal that sends a signal to the ovary to turn on initially. And then as it continues in that large non-pulsatile way, it turns off the ovary. I hope Dr. Maslow is not thinking I'm saying this wrong because this is-

Dr. Bat-Sheva Maslow:

No, you're doing a great job.

Dr. Elisa Krill-Jackson:

[inaudible 00:16:58].

All right, so how does estrogen work in the body? So estrogen and how does it affect cancer cells? So estrogen, so these little blue things up here in this slide that's supposed to be estrogen. Estrogen binds to estrogen receptors. So many of you with your cancer have probably heard your cancer's estrogen receptor positive or estrogen receptor negative. BRCA1 mutations are often associated with estrogen negative cancers that are not stimulated by estrogen. But most of our cancers, about 60, 70% of breast cancers even in young women are estrogen receptor positive. So the estrogen receptor sits inside the cell in the nucleus, the estrogen seeks it out, attaches to that. And then what happens once the estrogen binds the estrogen receptor is it tells the cell to go and do its thing. And that can be dividing, producing other things, but in a cancer cell, it generally tells it to grow and divide.

So how do we stop that? We give anti-estrogens. So there's two forms of anti-estrogen. Get rid of this. Anti-estrogen, there's selective estrogen receptor modifiers like Tamoxifen. How does Tamoxifen work? So I like describing this as a car with a key and an ignition, okay. So the estrogen receptor is like the ignition and estrogen is the key that turns on that cell. Tamoxifen is like a false key that plugs up that ignition and estrogen can't turn on that cell. So that works pretty well for most patients. It works for premenopausal patients and postmenopausal patients.

So there's another set of drugs called aromatase inhibitors. Now, aromatase inhibitors do not work on the ovary at all. In fact, the ovary has to be turned off for them to work. So somebody has to be in menopause, either natural or chemical, for aromatase inhibitors to work. They work by preventing the body from turning androgen, testosterone-like drugs that are produced in the adrenal glands and fat cells in the body. And that's normally used as the aromatase enzyme to turn it into estrogen to estradiol. So we use something called aromatase inhibitors that blocks that enzyme and the little bit of estrogen squeaking out from the adrenal glands and the fat cells is blocked. So basically what you're doing is you're taking away all the keys.

Then there's other drugs called selective estrogen receptor degraders, Fulvestrant. And we have new oral SERDS, including Elacestrant, which is... They're being looked at for curative treatment of breast cancer.

One of them, Elacestrant is being used in treatment for advanced disease. What they do is they bind this estrogen receptor and they degrade it. So they make it go away.

All right, what are the benefits of hormonal therapy? So they decrease the chance that the cancer will spread somewhere else and somebody will die of breast cancer. Now, how does that happen if somebody's had surgery? The problem with breast cancer and many, many cancers is by the time it's discovered, it may have sent cells to other parts of the body. So all our treatments that go to the whole body, the systemic treatments, what they are meant to do is kill any microscopic cells that have gone elsewhere in the body. Because when these cells are microscopic and just single cells, they respond very easily to treatment. They also decrease the chance that any breast cancer cells in the chest wall area will grow back into a new breast cancer and they decrease new breast cancer. So anybody who's had one breast cancer still has breast tissue, they're at risk for a new breast cancer.

So hormonal therapy is very, very, very important. And in fact, for many patients with estrogen-positive breast cancer, it is more powerful than chemotherapy. So menopause alone is not enough to treat breast cancer. Many post-menopausal women develop estrogen-sensitive breast cancer. In fact, the older you are, the more likely you are to develop breast cancer even if your ovaries are not functioning. Menopause alone is not hormonal therapy. It is part of hormonal therapy, but it is not sufficient and needs to be combined with an anti-estrogen to target the breast cancer cell or to remove that extra estrogen that's made outside of the ovary. We know that patients who use estrogen after diagnosis of breast cancer increase their risk of having breast cancer recurrence.

All right, so menopause, what are the symptoms? I'm sure many of you are familiar with them. Basal motor symptoms are hot flashes, irritability, vaginal symptoms, libido changes, weight gain, bone density loss, cardiovascular disease, joint aches, fatigue. So I'm sure many of you have experienced this and it isn't pleasant, but there's certainly ways that we can get around that. So what about hot flashes? So I spend a lot of time in my office talking about hot flashes. Fortunately, we actually do have a lot of medications that help hot flashes. The typical ones I prescribe on a daily basis are antidepressants like Venlafaxine or Citalopram, which is Effexor and Celexa. They work very nicely for hot flashes. They probably don't eliminate them, but they markedly reduce them. We know that acupuncture can significantly help hot flashes.

Then there's another drug that's not used nearly as much, but I actually think is probably more effective than the antidepressants called oxybutynin, or Ditropan, which is actually a drug that is used for bladder spasms. And it actually works really nicely in low doses for hot flashes with the main side effect being dry mouth. Gabapentin and exercise also help. And then there's a new drug called Veozah. So Veozah is FDA-approved just for hot flashes. It doesn't do anything else as far as we know. The problem with Veozah is I've yet to get an insurance company to pay for it, it's a relatively expensive drug, which is... It's really quite a shame. And I think we need to lobby our congressmen and everything because we all know that drugs like Viagra are paid for by insurance companies. But drugs for post-menopausal symptoms are very, very poorly reimbursed by insurance companies.

Vaginal symptoms. So again, we spend a lot of time dealing with vaginal symptoms. We're really fortunate at the University of Miami that we have a sexual health clinic. It's called a MUSIC clinic, which stands for Menopausal Urogenital Sexual Intimacy Clinic, and that's run by Dr. Kristin Rojas, who is a gynecologist as well as a breast surgeon. And if you look at this little QR code and take a picture of it, you'll get some information on her clinical trial that I'm going to talk about.

So vaginal symptoms, the most important thing we need to do initially if you know you're going to experience menopause even when it just starts, is to start using vaginal hydrators with hyaluronic acid in them. And the ones I've listed here have hyaluronic acid. They can be ordered online, they can be gotten at CVS. They're over the counter, they don't require a prescription, recommend them daily for a week or two and then twice a week. Things that are just soothing are Key-E, is can be bought at Amazon, is cheap,

which is a suppository of coconut oil and vitamin E. Coconut oil itself, Replens helps. Lubricants for intercourse is very important.

Now getting to the root of the problem of not having hormones to stimulate that vaginal lining, we can use vaginal DHEA. Again, it's a hormone, we try to stay away from that, but in people with intolerable symptoms, we can use it. Controversial also is vaginal laser treatment, the MonaLisa Touch. It does work for some women, but there are many people who are against that because it can be damaging when not used correctly. And then there's vaginal estrogen. So vaginal estrogen works exceptionally well for vaginal symptoms due to menopause. The problem with vaginal estrogen is some of it will get absorbed and there's conflicting studies on the safety of it. A study from Scotland and Wales a year ago showed no increase in cancer recurrences in women who took vaginal estrogen.

But last month at the European Society of Medical Oncology Conference, they showed a very large study looking at patients who had vaginal estrogen after diagnosis breast cancer. And they found that patients with estrogen-receptive negative tumors and people on Tamoxifen for estrogen-receptive positive tumors safely use vaginal estrogen, but there was about a 2% increase in recurrence in those treated with aromatase inhibitors. So in fact, I think the safety in patients who are on aromatase inhibitors is questionable. Look, people are looking at innovative ways to deal with this problem. And Dr. Rojas at University of Miami actually has a clinical trial ongoing using platelet-rich plasma, patient's own platelet-rich plasma injected into the vagina. And she's seeing some nice results from that. And obviously it's very, very safe for a patient.

Other things, symptoms of menopause include joint symptoms which we can treat with Cymbalta, exercise, acupuncture. But I think it's also important to talk to your doctor about changing medications. Even though we have three different aromatase inhibitors, some women will have severe joint symptoms due to one. I'll stop them, change them to another, and they feel much, much better. And sometimes we just have to stop the aromatase inhibitor and switch them to Tamoxifen. Although Tamoxifen is slightly less effective, it doesn't cause those joint symptoms.

The other thing is there are currently ongoing clinical trials which are looking at that other class of agent, the selective estrogen receptor degraders. They're looking at giving that instead of aromatase inhibitors or giving that and switching from an aromatase inhibitor. So those are potential clinical trials for somebody who may want to consider a change. Now those are randomized clinical trials right now, half the patients will stay on their aromatase inhibitor and half will switch. But I think it's a worthwhile thing to do. We think these drugs are very effective and potentially more effective than an aromatase inhibitor.

I'm sure, as you know, there's a lot of psychological symptoms associated with menopause. Alona discussed some of them. Irritability, fatigue, brain fog. These are much harder symptoms to deal with. Obviously the irritability and depression is generally well-treated by antidepressants and we find that Wellbutrin actually can help energy as well as mood. Acupuncture again is helpful. Exercises are helpful, psychological counseling, and sleep hygiene. I've had a few patients who have relatively taxing jobs, intellectually taxing jobs who just can't focus. I've selectively used low-dose stimulants in them like Adderall and they find them very, very helpful. But it's a very few patients that I've used that in and it has helped.

Anyhow. So that is the symptoms of menopause and how I deal with that in my patients. Obviously, we want patients to be cured of their breast cancer and menopause is a big part of that, taking away that estrogen that's stimulating those cells or people just go into menopause because of the chemotherapy or because they need their ovaries removed because they have BRCA mutation. So there's many, many reasons that we unfortunately have to put women into menopause to improve their prognosis. But again, I find that with a lot of work with my patients and openness, we're able to solve a lot of these problems.

I ask all my patients if they're having vaginal symptoms because people are afraid to tell you if you don't ask them. So I think it's something that you need to know to bring up to your doctor even if you're not asked. And if you don't get satisfaction, you should talk to somebody else. But again, oral estrogens are

generally not safe after a diagnosis of breast cancer, perhaps in very unusual circumstances, but we try to avoid them. And like I said, I think we do have very good medications to help other symptoms to make patients feel as good and healthy as they can and make life actually Very good. Thank you.

Melissa Rosen:

Thank you so much. Dr. Krill. You actually answered a great deal of the questions that were asked about managing menopause symptoms. And [inaudible 00:31:34] back for the Q&A. Now I want to add Dr.... Spotlight, there we go. Our next doctor, our next presenter is Dr. Bat-Sheva Maslow who will be speaking about fertility preservation and the cancer experience. Dr. Maslow completed her OB-GYN residency at the hospital of the University of Pennsylvania and her Reproductive Endocrinology and Infertility Fellowship at the University of Connecticut School of Medicine. She's passionate about educating her patients. This is why it was such a good match. They're both very passionate about educating their patients on the reproductive options and sitting with them in their most vulnerable moments. She practices out of RMA, New Jersey's Basking Ridge and Jersey City offices. Dr. Maslow provides RMA patients with a full spectrum of fertility care specializing in egg freezing and fertility care for orthodox Jewish patients. She approaches patient care with education, honesty and compassion. Dr. Maslow, thank you for being here and the screen is yours.

Dr. Bat-Sheva Maslow:

Thank you so much for having me. Everyone can hear me okay? Perfect. I decided this time not to share slides. I think for this type of topic, especially with there's going to be so many questions, I'm hopeful that just in a conversational manner we can cover some of the most important topics to address related to fertility preservation with respect to cancer.

And so I just want to get started by covering a few real basic understanding of fertility in general and then I'll get a little bit more specific. So whenever we're talking about anything related to fertility, the number one issue, the number one through three top issue is always going to be the age of the female partner. And this is true whether there's a cancer diagnosis or not. Just like Dr. Krill mentioned that menopause is a part of life, the reality is is that infertility is also a part of life. There is a time at which every female will become infertile. The question is she actually trying to conceive at that time?

And infertility and menopause in their natural state are really part of a spectrum. So like Dr. Krill mentioned, over time the ovaries start to decline and the quality and the quantity of those eggs will get to a threshold in which a woman is no longer able to conceive well before her periods end, well before the ovary completely stops functioning, well before the ovary stops producing estrogen like Dr. Krill mentioned. So women are born with all the eggs will ever have, millions of them, and over time our egg supply will decline. And eventually when the eggs run out, that communication between the brain and the ovary will cease and the periods will stop and a woman will be in menopause.

However, more importantly for fertility in terms of conception, what happens over time is that damage starts to accumulate in the egg itself and the egg's ability to start separating its chromosome because an egg has to have half the number of chromosomes of a normal cell. That process starts to break down and what you end up having are eggs that have either too many or too few chromosomes. The medical term for that is aneuploid. They have abnormal number of chromosomes and these abnormal eggs tend to just not work. So they will typically ovulate and either not fertilize or not implant. Or occasionally they will implant, but the end is an early miscarriage.

And so that is the predominant reason that women will experience infertility at higher rates as we get older because as the eggs age, more of them will start having these abnormalities. And so month after month, the egg that ovulates is more likely to be abnormal as a woman ages. That is a truth of life. Now, that process varies widely from person to person. So we know if we look at big populations, we will see this very nice decline that's pretty straightforward. But if you look at an individual, it's all over the place.

And even if you take groups of individuals at any given age, you're going to have a very wide range of both egg supply and response and egg quality and the ability to conceive.

And so there's a lot of variability from person to person and there's a lot of variability over time. And so it's not nearly as predictable as we would like in any circumstance. Which is why just even outside of the realm of talking about cancer diagnoses, the whole concept of fertility preservation of egg freezing for women who may not be able to conceive for whatever reason has born out of the discussions of fertility preservation with respect to cancer and has become very widespread. The reason being is that fertility can be so unpredictable even in a natural setting, let alone when you start adding other things like cancer and cancer treatments to the mix.

So the age at which somebody is, A, affected by cancer, B, trying to preserve their fertility, and C, trying to conceive are all very important factors when it comes to this discussion. What makes it so much more intense and so much more relevant, and Alona, when she described her story really hit upon so many of the important points and experiences that my patients go through when we have these conversations, is that the effects of chemo and potentially radiation can be very profound on the ovaries.

The thing is that the chemo itself is geared towards trying to impact rapidly dividing cells. The eggs themselves are actually not rapidly dividing, they barely divide at all prior to fertilization, but they are surrounded by cells that support them. We call them granulosa cells. Those cells actually are quite rapidly dividing. And so the chemo actually profoundly impacts the granulosa cells. And if enough granulosa cells are affected by the chemo, then the egg that they were supporting will die out.

And so the one reassuring piece to take out of this is that eggs that survive the chemo process generally are protected from the untoward effects of chemo. So what we don't see is an increased rate of birth defects in babies born to women who have received chemotherapy. And so we know that the eggs that actually make it and survive through are not deeply affected by the chemo themselves. But what we do know unfortunately is that the chemo itself eradicates a large percentage of the egg supply. And so if someone starts off here, let's say at 28, their egg supply is at its peak, and naturally they would decline this way. If you put chemo in the mix, you end up with, it goes like this, and then their age picks up. So they've lost somewhere between 30 to 70% of their egg supply and then age still progresses. So the impact of time will continue to progress and now you're at a much lower amount.

It is thankfully uncommon that women will be put into permanent menopause as a result of their chemotherapy. It was much more common in years past when chemotherapies were more intense and less highly specified. It is less common now. It is less common the younger women are when they are diagnosed and treated. So younger women are less likely to be put into permanent menopause by their chemotherapy than older women. Really the closer you are to natural menopause, the more likely it is that the chemotherapy is going to induce menopause. Because depending on where you are on this slope, the closer you are to the bottom, the more likely it is that the chemotherapy is going to bump you into the bottom.

But it is extraordinarily common that women will experience menopausal symptoms during their chemotherapy. The communication between the brain and the ovary is highly nuanced and highly sensitive to the things that are happening in the body. And when the body is under a lot of stress, that whole system can totally shut down. And so even women who don't take Lupron, which I'll touch upon in a moment, may experience a sort of temporary menopause where they don't get periods, they get all the symptoms that were described, but it tends to rebound sometime between usually three to nine months after completing chemotherapy and their cycles will return.

But as Alona mentioned, cycles returning is not necessarily synonymous with fertility and the ability to conceive. And so we know that women who are exposed to chemotherapy and/or radiation are at higher rates for infertility than other women their age who have not been exposed to chemotherapy and radiation. Even if their periods return, even if all their testing appears normal, we know that they're at higher risk for

infertility because a whole portion of their egg supply and a whole portion of their reproductive system has been affected by the chemotherapy.

And so on the one hand, what is helpful to know is that it's not necessarily, it's not 100% that someone will experience infertility after receiving chemotherapy or radiation. It is very high, but it's not 100%. So there are lots of amazing success stories of women who go on to have babies of their own without requiring any kind of assistance. It is dependent particularly on the age at which women are exposed to chemotherapy and the type of chemotherapy they're exposed to. So certain chemotherapies are more what we call gonadotoxic, they're more toxic to the ovaries than others.

One of the things we can do, as Alona brought up, is that we can use Lupron, which is a way of sort of preemptively quieting down and shutting down the reproductive system to protect the ovaries from the effects of chemotherapy. Now, it is by far not perfect because if it was perfect, we would use it all the time and we wouldn't even be talking about egg freezing and embryo freezing and all these other things. So it is not perfect. But what it does is by quieting down the communication between the brain and the ovary and quieting down the ovaries function, you get fewer cells that are active, fewer eggs that are active, fewer granulosa cells that are active, so they are less susceptible to the effects of chemotherapy.

And so it does improve outcomes, but it's by no means perfect. And so what that leads us to is thinking about opportunities for fertility preservation, which would mean freezing either eggs or embryos prior to the exposure to chemotherapy. Before I touch upon what that looks like and what that means, the one last piece of critical broad information that is important to know when we talk about this is that when you do have frozen eggs or frozen embryos, one of the most mind-blowing things that's possible is that you can get pregnant after menopause. So if you have eggs or embryos that are frozen, they can remain frozen indefinitely. You just heard a story about an egg that became a baby 12 years after it was retrieved.

These eggs and or embryos can remain frozen indefinitely. They don't age. And so even though the body ages, even though that person may transition into menopause either naturally or prematurely because of her chemotherapy or abruptly because of surgery, having the ovaries removed, if you have frozen eggs or frozen embryos, we as physicians can actually induce a safe and healthy pregnancy without ever having to touch the ovaries. As long as a uterus is intact, we can create an environment in which a pregnancy can be successful, which is mind-blowing on so many levels, but it's one of the most amazing things that, especially when we're talking to women who have undergone treatment for breast cancer, is important to remember and people don't always realize.

So those are my three fundamental knowledge pieces that we need to know. Age is critical. The way chemotherapy affects the eggs and thereby affects fertility. And that you can have pregnancy after menopause if you have preserved fertility in some way. To finish up, I want to touch upon two more things. So one, fertility preservation. As Alona mentioned, fertility preservation was always the standard of care. Thankfully now, more and more it is becoming something that is very standard. Most oncologists are very familiar with the ins and outs of fertility preservation.

And depending on the case, you are often capable of being able to take some time to do the fertility preservation. It typically can be done in about two weeks many times, especially if I have patients who are breast cancer patients who are having their surgery first. Now, obviously every protocol is different, but let's say the group of patients who often have the surgery first and then are having follow-up chemotherapy. That period of time between surgery and chemo is actually a beautiful time to do fertility preservation because there often are a few weeks in between. Sometimes if we're having a patient who's doing neoadjuvant chemotherapy, we can delay the chemotherapy by a week or two or three in order to be able to do a fertility preservation cycle.

The cycles take about 10 to 12 days of medications. The medications we use are the same hormones the brain is using to regulate the menstrual cycle, the FSH and LH that Dr. Krill mentioned. We give them as injectable hormones every day for 10 to 12 days. It's definitely an intense process. We do very frequent

monitoring. So we have these monitoring visits where patients come in for blood work and ultrasound every few days so that we can really custom tailor the protocol to each patient's response.

Particularly for patients who are either at risk or who actually have a diagnosis of breast cancer, we'll often use an aromatase inhibitor like Letrozole, which decreases circulating estrogen levels. So the estrogen levels are going to rise temporarily as the ovaries are stimulated and we can medically reduce the risk of the exposure to those elevated estrogen levels. There have been some really, really great studies coming out of Europe that have looked at the risk to long-term recurrence in women with breast cancer having done any type of fertility preservation prior to their treatment, and it really does not seem to affect their long-term outcomes. And so we can feel very reassured by this that these temporary opportunities to freeze either eggs or embryos are safe and effective.

Now, the things I always warn my patients, there's a lot of variability and it is very hard to predict. So just like Alona mentioned, her egg freezing process was very disappointing at first. Two eggs is very disappointing. When we're doing these types of fertility preservation cycles, we're not always able to do them under optimal conditions. The body is already taxed because it's being exposed to cancer and other types of medicines and medications, potentially surgery. So the body's already taxed and so reproductive system's already taxed by definition just because it is so sensitive to the rest of the equilibrium of the body.

And so we don't always get the numbers of eggs that we would typically expect based on age and blood work and other things, but it's often still worthwhile. When we freeze eggs, we really can't predict what the likelihood is that any one egg will go on to produce a healthy baby. We know that there's a lot of inefficiency in human reproduction, and so not every egg is going to fertilize and not every egg is going to become an embryo and not every embryo is going to become a baby. And so ideally we want to freeze as many eggs as we can, but sometimes we just freeze what we can get. I've heard plenty of stories like Alona's where we have fewer eggs than we would expect and they get discounted and it's like, "Oh, there's no point." And actually one of them becomes a baby. The younger those eggs are, the more likely it is that any one of them could go on to produce a healthy baby. So a 28-year-old, those eggs could potentially be very successful. If that was a 38-year-old, it would be much less likely.

Embryo freezing allows you to have a little bit further down the process, so the eggs that wouldn't make it to embryos, you're not freezing, so you have a little bit more confidence in what you have. Those embryos can also be tested for abnormal chromosomes so you can have an idea of how many of the embryos you made would never have worked in the first place. And so you can feel again more confident about what you have frozen. The challenge with embryo freezing compared to egg freezing is, one, you need a partner for it and not everybody has a partner. The other is that if you make those embryos with a partner, those embryos are, for lack of a better term, owned by the two of you, and generally speaking, they really can only be used within the context of that relationship.

There are some pretty sad stories that have gone through the court system. One that included a woman, she was actually a physician in Arizona who froze embryos with her husband prior to her breast cancer treatment. They then got divorced. She then got remarried. She was relatively young, but her fertility had been compromised by her treatment. And she no longer had access to her embryos that she made with her first husband and he would not allow her to use them. And the court systems generally will favor not using them outside of the relationship that created them. So eggs give you a lot more flexibility, but embryos give you a lot more confidence and really in each circumstance has to be judged and discussed with an expert and figure out the best system, the best approach.

The last thing I want to say, because I know I'm running out of time, but the last thing that I want to say. Actually two more things that I want to say. Sorry. The last thing that I want to say is particularly related for cancer-causing mutations, so BRCA, any of the other potentially cancer-causing mutations. There is a very important role to consider for fertility preservation and assisted reproductive technologies like IVF for anyone who carries one of these mutations, whether or not they have themselves been diagnosed with

cancer because we now have the technology that will allow us to test the embryos for the particular mutation.

And so what that means is let's say you have somebody who's a BRCA carrier, whichever one, and whether or not he or she has been diagnosed with a cancer themselves, they can actually identify which of the embryos they made carries the mutation. And if they so choose, they can utilize the embryos that don't carry the mutation. In the case of BRCA, where it's what we call autosomal dominant, where there's only one copy that induces the effect. If everybody could do this, which we know realistically everybody can't, but if everybody could do this in the whole world, you could essentially obliterate the mutation in one generation.

Now, it's theoretical because not everybody's going to be obviously able to do it and not everybody's going to necessarily create embryos that don't have the mutation or 50% of the embryos will have the mutation statistically. But theoretically, you can abruptly stop the mutation from being passed down in your family by utilizing this technology. Now, it's not as simple as I'm describing. I'm oversimplifying a little bit, but I want to make sure that it's clear that that is a possibility. And so what I see a lot of now more and more are couples or individuals who are coming to me who know that they carrier, they have family members who have been deeply affected by the mutations and they want to have the opportunity to have children who do not carry this mutation.

And the most important thing to know when we're utilizing this technology is because 50% of the embryos are going to carry the mutation. Whether the mutation is coming from the mom or from the dad, statistically half the embryos are going to carry this mutation. The age of the woman who's contributing the eggs is the critical piece here, and I know I started with that, but it is so important because as you get older, more of the eggs are going to have other abnormalities that don't make them viable. And so once you're starting to look for, you want both a viable embryo and one that is not a carrier of the mutation, it becomes exceedingly hard as you get older. So in a 20-something year old or even an early 30-something year old, it's actually relatively easy, but if you are looking for a non-carrier and a healthy embryo at 38, 39, 40, it becomes exceedingly difficult. And so to be proactive and to think about this proactively actually can be very beneficial whether or not you're diagnosed with the cancer.

And the last piece I'm going to close with is just about getting pregnant after cancer treatment. And this could be a lecture all into itself, but by and large, those same groups that looked at in Europe that looked at women who did any kind of fertility preservation prior to treatment, they're also looking at studies where they're giving women opportunities to take breaks off of their hormone disruptors to get pregnant. For a short period of time, get pregnant, and then go back on them. And they're having excellent results. There's a lot of reassurance to support that there are safe ways to be able to have and grow your family even within a few years of having completed your cancer treatment. And that can be a real source of strength for patients.

One of my very first patients when I graduated fellowship was a young woman who was diagnosed with breast cancer in her early thirties. She came to me with her husband. We froze embryos for them, she underwent her treatment. Several years later, she came back to me to get pregnant. She took a break from her medications, from her Tamoxifen treatment. She did an embryo transfer, she got pregnant, she had a baby. And now it's been a few more years. She just came back for her second child. And she's doing the same thing, taking another break from her treatment in order to have baby. It's really remarkable that we have these opportunities now. Her story went smoother than others, but there are amazing opportunities.

She's also at the age now where she's being recommended to potentially remove her ovaries. And she doesn't have weigh this difficult decision of do I remove my ovaries when my doctors think that it would be most safe for me to do so, or do I keep pushing it off because I want to keep having children? That's a horribly difficult dilemma that a lot of my patients struggle with that by having frozen eggs or embryos, you can actually detach those two things. You can have children when it feels right and when your

doctors think it's safe and you can remove your ovaries when your doctors recommend it. And they too don't necessarily have to be related. And it's really quite remarkable that we're able to do that safely now.

And that's very briefly touch upon all the major topics related to fertility preservation and getting pregnant after treatment.

Melissa Rosen:

So I want to thank you. That was a lot of information and now we have a good news, bad news situation. The bad news is that we don't have time for a lot of questions. The good news is that both of you managed to answer a lot of the questions that were asked. So we're going to ask each of you one or two questions and then we have a couple of more really important points to conclude with and we're done. So I think we're going to start with Dr. Krill. Can you talk a little bit... You've talked a lot tonight about managing the immediate side effects of menopause, but what about those long-term side effects? What are the effects of going into menopause surgically or chemically very early? How do they differ from naturally-occurring menopause? And more importantly, how are we managing brain fog for that many years, the stiffness of cardiac muscle for that many extra years? Things like that. What are the risks there and how do we manage those risks? And I'm going to ask you to answer really shortly.

Dr. Elisa Krill-Jackson:

Okay. So that's a really excellent question, and I'll talk really fast. We do have to make sure your heart is good. You need your cholesterol checked, you need to manage your cholesterol, manage your blood pressure, because we know in menopause you have higher risk for cardiac disease as well as on the aromatase inhibitors. Brain fog doesn't usually last forever. Honestly, I find most women do fine after short amounts of time with exercise and the farther away they are from chemotherapy. Most of us over the age of 50 live with menopause anyhow. And we do fine. I still function fine. Usually those symptoms get better. Bone health, we usually give bone-modifying agents with... If we put somebody in menopause, we give bone-modifying agents, number one, to make sure their bones stay healthy. But number two, it decreases the risk of cancer metastasis in the bone. So there's a lot of things we can do.

Is life different? Yes, sure, life's different. Is it still excellent? Yes, we can make your quality of life excellent. And just to add to what Dr. Maslow said, if anybody wants to look up one of the trials, there was a large trial in the US called the POSITIVE Trial, which showed that women after taking two years of hormonal therapy could stop and they monitored them while they tried to get pregnant, had a baby, and most of them were able to achieve a pregnancy. Most of the people who achieved a pregnancy had a baby, and compared to historical controls, there was no increase in women dying of breast cancer or having distant recurrences. It's called the POSITIVE Trial, if you want to look it up, it was run out of the Farber and it was just presented at one of our major conferences about a year ago.

Melissa Rosen:

Thank you. Thank you. Dr. Maslow, can you touch briefly on this, at least relatively new to me information, then in addition to these challenges that you've talked about, that women who carry BRCA mutations may have a reduced egg reserves, and how might that impact the decisions they need to make regarding fertility?

Dr. Bat-Sheva Maslow:

So this is an old concept that became new again. It's one of these things that makes its way pendulum swinging back and forth through the various research and trials. It's still, I think I would say is controversial whether the BRCA mutation actually has a direct impact on egg supply. There were some initial studies that suggested that women with BRCA mutations have lower egg supply overall compared to their age match peers. And therefore when they do some kind of egg retrieval process like egg freezing

or embryo freezing or IVF for getting pregnant immediately would have lower egg yields. And then there were lots of other studies that demonstrated that that just wasn't the case. So I think it's still a little bit up in the air.

Physiologically, it doesn't really make sense. The pathways that the BRCA mutation work don't really implicate the egg supply and doesn't really quite make sense. I think it's more that we're seeing that the more we learn about egg supply, the more we realize how variable it can be and how we don't yet really know what is normal. And so we see the more we're looking at egg supply in different populations of women, the more we're going to see wide variations. We don't yet know are there differences in egg supply based on ethnicity, based on other health factors that we haven't really discovered that maybe run parallel with women who might be at risk for carrying BRCA. I think it is still definitely an area that needs to be explored more.

My take home from that is that especially women who carry BRCA who might want to have a family in the future, the proactive conversations they can have with a fertility specialist even well before they're planning a family so that they can understand what is my fertility? What does my egg supply look like? What are my options? What should that timing look like? How urgent is this? How non-urgent is it? Those types of things are really important. And I say this to all of my patients, whether they carry genetic mutations or they are single or they are married or they are infertile, knowledge is power.

And so being able to think proactively and recognize that there may be a problem well in advance of it affecting you, gives you the opportunity to make decisions proactively rather than reactively. And so even though it's so hard and you're coming at a position that is so vulnerable and there are so many things being thrown at you, so I understand the anxiety about learning about one more thing that might be wrong, but really it gives us the opportunity to make good choices and potentially improve the opportunities to achieve all those family goals that we want for all of our patients.

Melissa Rosen:

I think a great place to end is proactively versus reactively wherever possible. I wish we had time for more questions. I really do. Like I said, a lot of them were asked already. One thing I want to note about questions, there were a lot of questions that came in earlier about sexual health. We intentionally did not address those evening because our next... Right in the chat box right now is a link our next in this series, which is the evening of July 17th, again, sexual health and intimate relationships. We'll save those questions for that. And there were some questions that came in also that we really believe required a one-on-one conversation. And so one of our clinicians will be reaching out to the authors of those questions. As we conclude, I want to offer many, many thanks to Alona for sharing her story and to our two fabulous experts, doctors Krill and Maslow for providing guidance on these incredibly important issues. Thank you again today, Daiichi Sankyo, Pfizer, and the CDC for their generous support.

To make it very easy for you to register for the next in the series, we have a QR code. The link was in the chat box, but there's a QR code to scan if you'd like to register right now for that. And please take a moment to click the evaluation link in the chat box now. Again, it'll take just a moment and you will be able to continue to listen. And finally, I want to remind you as we conclude that Sharsheret continues to be here for you. Our social workers as always, are available to answer questions, provide support, and connect you to resources. Tonight's topics are difficult ones, emotional ones. Please don't hesitate to connect with us for support. And you can reach our social workers through the email in the chat box. There's also an opportunity to request a connection with one of our team members in the evaluation. Again, let's put the evaluation link in one more time. I want to stop my share, but that doesn't seem to be happening. There we go. Thank you for joining us and have a wonderful night. Good night.