Breast Cancer and Fertility Symposium Transcript

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Weill Medical College of Cornell University
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Presented By:
Sharsheret and Fertile Hope

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I. Introduction

ROCHELLE SHORETZ: Good evening, everyone. Thank you for joining Sharsheret and Fertile Hope as we present our first Symposium on Breast Cancer and Fertility.

I'm Rochelle Shoretz, Executive Director of Sharsheret, and I will soon have the pleasure of introducing Lindsay Nohr, Executive Director of Fertile Hope.

When I was diagnosed with breast cancer a little over one year ago, I was overwhelmed with concerns. What type of surgery would I require? What course of treatment should I choose? Will I lose my hair? Will I live?

At age 28, with two young boys at home, I did not even consider the effects of breast cancer treatment on my ability to have more children. Nor did fertility appear to be a major concern for my health care team. Not one of the five doctors with whom I consulted before treatment began called issues of fertility to my attention, referred me to a fertility specialist, or even suggested that I consider the effects of my decisions on the ability to have children in the future.

I brought with me tonight the book in which I kept notes of the discussions I had with my doctors. I'd like to share with you the knowledge I had about breast cancer and fertility before I made my surgery and treatment decisions.

I met with two breast surgeons and a reconstructive surgeon before I even thought to raise the subject of fertility. Here are my notes on that discussion:

"Further childbirth. No further pregnancies because high estrogen state. Egg retrieval problematic for timing."

A few weeks later, an oncologist with whom I consulted added to my knowledge the following: "Egg harvesting. Viability of eggs not clear. Treatment with hormones stimulates breast cancer. Potentially dangerous."

And then this, a few days later, after a discussion with another oncologist. "Chance of successful pregnancy not much different than taking chance post-chemo."

Despite the lack of information I carried into treatment, I consider myself fortunate to have even entertained concerns about fertility. Many of the young women who call Fertile Hope or Sharsheret are not as fortunate. These are women who are swept up in the flurry of decision-making post-diagnosis, particularly rushed for young women whose cancers are often more aggressive.

Decisions are made; surgery is completed, treatment begins, and the dust begins to settle. It is then that many young women begin to wonder if they will be able to have children in the future, a question they should have been told to ask from the start.
Our aim tonight is to present the latest information about options for preserving fertility before treatment, the effect of breast cancer treatment on fertility, and the role that Tamoxifen plays in fertility. A panel of world-renowned experts will share their insights on these important topics.

We will then hear from representatives from support organizations addressing the needs of women concerned about breast cancer and fertility. Our panelists will take questions from the audience, and then we invite you to join us at a reception in the adjoining lounge.

Our hope is that the presentations tonight answer some of your questions, raise new ones, and generate discussion about breast cancer and fertility among health care professionals and patients. Our hope is that the presentations tonight offer not only information, but options for support for young women living with breast cancer and their families who are concerned about fertility.

And *my* hope is that the presentations tonight allow young women to fill their own books with more information than mine included.

Thank you all for joining us, to our panelists for sharing their time and insights, and to all of the symposium sponsors for their support this evening. And you can find a list of our generous sponsors on the back of the program you received when you entered the room.

It's now my pleasure to introduce Lindsay Nohr, Founder and Executive Director of Fertile Hope, a national not-for-profit organization providing information and support regarding cancer and fertility.

Lindsay is tireless in her efforts to increase awareness, education, and research on the needs of cancer patients whose treatments present the risk of infertility. So many of the women at Sharsheret have benefited from her guidance, and on their behalf, I thank you, Lindsay.

II. The Effects of Breast Cancer Treatments on Fertility

LINDSAY NOHR: Thank you for a kind introduction, Rochelle. It is with great honor that I can introduce our keynote speaker, Dr. Zev Rosenwaks.

As the Director of the Center for Reproductive Medicine and Infertility at Cornell, Dr. Rosenwaks is a world authority in reproductive endocrinology and infertility. Not only is Dr. Rosenwaks a founding pioneer in assisted reproductive technologies, but he is dedicated to using his expertise to benefit cancer patients facing infertility. Dr. Rosenwaks.

DR. ZEV ROSENWAKS: Okay, so I'll add another gadget to my belt. Thank you, Lindsay. It is a pleasure to be here. I wonder how many of you know what Sharsheret means?

Okay. Well, then I will start my talk by telling you that what I'm here today, is -- and I just thought about it -- is to talk about fertility preservation in breast cancer patients. And I will use a Sharsheret, a chain, or a necklace, to illustrate what I will talk about.

I'll talk about the ovary and its follicles, and how we like to preserve some follicles, to preserve reproductive function. Mention something about egg freezing, and a little bit about embryo freezing, and how it can be used in patients with cancer to preserve reproductive function.

Dr. Oktay will talk to you about some very exciting work on tissue cryopreservation, and the use of Tamoxifen, again, specifically for breast cancer patients. And finally, I will give you a little glimpse into the future, where we think we might be able to solve the problem of infertility both for cancer patients who lose their reproductive function and for women who have no ovaries at all.

Now, of course, the good news is that we have come a long, long way, in cancer therapy; that indeed we do have the issue of preserving reproductive function. Because we know that improved survival rates after treatment of many cancers in patients that occur in patients of reproductive age, and that infertility and gonadal dysfunction are common sequelae of many cancer therapies, including therapies for breast cancer.

In the female, of course, and this occurs, of course, in male and female, but in the woman, in the female, we worry about decreased egg numbers, losing eggs, and of course, in losing hormone production, menstrual function, and of course, the sequelae of losing hormonal production. And that's another major concern besides fertility.

The effects of cancer therapy on fertility are very much dependent upon the age of the woman at the time of treatment, the chemotherapy drug, that is, the type of chemotherapy, and the total dose. And in other cancers, of course, radiation therapy field and total dose, but that really won't be discussed today since [of course the breast] [phonetic] is out of the field of radiation to the pelvis.

Breast cancer is really an important issue with regard to preserving reproductive function, because it probably is the most common cancer in women of reproductive age. It affects 185,000 women per year in the U.S., and in fact, 25 percent of all cases occur before the menopause.

And this is one of Anne Moore's diagrams and a pie looking at ten years of breast cancer cases at New York-Presbyterian Weill Cornell Medical Center. In over 5,000 cases, we note that 17 percent of all these patients were less than 45 years of age. 17 percent.

And another 28 percent are between 45 and 54, and you'll see, that when we talk about menopause, really the average age of menopause is 51 to 52 in the United States, so even these women have some reproductive function. And that's a concern in terms of hormonal production and potential problems with premature menopause.

We know also that adjuvant chemotherapy, CMF, and [I do mention] [phonetic] Cyclophosphamide are helpful in prolonging survival of breast cancer, but they also contribute to the development of premature ovarian failure. With this protocol, CMF, 77 percent -- according to Goodwin -- actually develop ovarian failure, menopause, and 38 percent with this therapy.

But in fact, it is the alkylating agent, Cyclophosphamide, Cytoxin, really, that is responsible for the problem, for the most part. And in fact it's probably the total dose in this regimen, the lesser of dose, and only four doses in a certain period of time that is responsible for the lower incidence of ovarian failure.

Now, what determines the risk of developing menopause with adjuvant chemotherapy? And again, to go back to the general slide I gave you before, it's the type of chemotherapy; very importantly, the age of the patient, and of course, the cumulative dose of the chemotherapy. One cannot underscore this enough. The type of therapy, the age, and the cumulative dose.

I'll show you some examples both from human and from animal work. This is a slide from Meirow [phonetic], and Dr. Oktay actually lent me this slide, and I should tell you that not one but several of these slides will be Dr. Oktay's.

But that's to emphasize, again, that if one looks at the relative or the odd ratio, relative impact on ovarian failure of various drugs, it's important to note that alkylating agents are the biggest culprit in destroying reproductive function. And of course, they are used for breast cancer adjuvant therapy.

Age. Why is age so important? If a drug is to destroy follicles, it will destroy a proportion of the total follicles that are present in the ovary. And this is a slide from [Fateh Gazun's] [phonetic] work showing the number of follicles per unit area in the ovaries by age. Birth, 10 years, 20 years, 30, 40, and so on.

Note there is a fairly predictable decrease in number of follicles per unit area throughout life, and its slope is very predictable, up to around the age of 37. And at the age of 37, the relative decrease, the proportionate decrease, is even greater. And by the time a women reaches the age of 51, 52, she has practically no follicles left.

Clearly, if you were to get chemotherapy at this point in one's life, you could see how more likely it is that one would develop ovarian failure than when you have lots and lots of follicles and you get chemotherapeutic treatment.

This is a work from Meirow in the rodent, basically showing that at any stage, even early follicles, primordial follicles, when they're exposed to chemotherapy - in this case, Cyclophosphamide, again, the alkylating agent – the follicles get destroyed.
More importantly, and perhaps most significantly, when you look at the number of eggs per, again, specific area in the ovaries, and looked at the dose of the drug, the greater the dose, of course, the larger and more significant was the drop in the number of follicles. A very important and significant study, clearly illustrated right here.

So, total dose is extremely important. How does that translate in terms of what we see and what we tell patients? How can we tell a patient whether she has a problem, or had a problem, or will have a problem with a particular medication therapy?

Well, this is a little complicated but it is not as complicated as it seems. And incidentally, I actually made this slide so I'm kind of proud of it.

Take a young woman who has no particular problems; this is her ovary. She's got lots of follicles. Most of the follicles are not visualized; they're primordial; they're microscopic. But if you were to do a cross-section, take a cross-section of her ovary, she would have certain actual follicles, follicles with some fluid in it, that you could see on ultrasound or you can see, if you were to cut the ovary, you will see it at the ovary.

This ovary would produce estrogen and some protein hormones called inhibitins. The reason inhibitin is called inhibitin is because that protein product from the ovary suppresses the pituitary production or secretion of FSH. Are you all familiar with FSH?

FSH is Follicle Stimulating Hormone. There is a language, a communication, established between the pituitary gland and the ovaries such that estrogen is the language that is spoken by the ovary. It feeds back through the bloodstream to the pituitary. It tells the pituitary, "I'm doing okay, I don't need any more push, stop giving me the FSH." FSH goes down.

FSH drops; follicles in the normal young woman, a single follicle, will develop. As one gets on in age, and as you recall, after the age of 37 when the follicle number decreases, the ovary is not as capable of producing estrogen and inhibitin. And it tells the pituitary, by virtue of the bloodstream, that estrogen production is very low. And the pituitary, in order to push the ovary, increases the FSH level.

In the menopause, when there are no follicles remaining, there is no estrogen, or very little estrogen, very little inhibin. It feeds back into the pituitary and the pituitary pushes the FSH up to levels that are greater than 40 [milli] [phonetic] international units per ml. And that's how menopause is defined.

The thing that we're worried about in the context of chemotherapy and preserving reproductive function is can we use FSH levels to determine if a woman still has some follicles, and can she still be rescued? And in those instances, of course, the FSH won't be 40; it might be 20. It might be 18. It might be 15. So we can determine a woman's ovarian reserve by looking at her FSH level.

The menopause, once you reach it, it's too late. We can't do very much for women in the menopause in terms of reproduction, except when we talk about the future, and that is, if we were able to manufacture eggs.

So I wanted to put this concept out, because oftentimes when you present to the physician and talk about reproduction, they only talk about menopause. And many of the papers, and one paper I will show you, will talk about menopause, but menopause is at the end of the line. There are those periods in between which really are the periods that we are most interested about.

Another important concept to reiterate is that in chemotherapy, the impact on gonadal function is very important. And to reiterate again, that in this CMF - the classical adjuvant treatment for breast cancer - we get the most dysfunction and the greatest destruction to the ovaries. Whereas in adjuvant Adriomycin and Cytoxin we get maybe half the destruction, as I showed you from the studies of Goodwin.

Similarly, in Hodgkin's disease, if we use MOPP protocol, versus ABVD, again, both in males and females, you get most severe problems with these regimens comparing these regimens. And this is a slide that Anne Moore lent me. I think it illustrates this extremely well.

Now, as I mentioned before, one of the things we worry about is menopause when we – in other words, premature menopause, the destruction of ovarian function. Now, this is from a study of Goodwin showing that if they looked at women that had no treatment at all, they noticed that if you looked at the probability of menopause, the older the woman got, of course, the higher the probability that she would be menopausal. That's very clear. And very few women were menopausal before the age of 40, and certainly very few even before age 45.

These women received, according to at least the work by, at least the description that Goodwin suggests, Tamoxifen treatment shifted the women so that menopause occurred earlier. I'm not sure that that was the case, because they did not measure FSH; they only looked at amenorrhea. And Tamoxifen itself can cause amenorrhea by thinning the lining of the endometrium. So this may not really be a relevant point in terms of potential reproduction.

However, when they looked at women who had chemotherapy, it was clear that the shift to early menopause was evident, quite significant, and you see that at any age, just about, when you get chemotherapy, you will have the development of ovarian failure – of some degree of ovarian failure.

I think this is a very elegant study, and I think these graphs illustrate this probably better than anything else we have seen in the literature.

I've already mentioned what is stated in this slide, basically, but that I believe that amenorrhea, as described by Goodwin, was not – they used amenorrhea but not FSH as a marker. And of course, if you go back to the slide you'll note that in women that were younger, there was no difference with Tamoxifen. Tamoxifen probably did not cause any problem. [Technical comment, not transcribed.]

The marginal increase occurred only in women who were 35 years or older, and as I mentioned, Tamoxifen can cause functional amenorrhea and was also given to periomenopausal women, and probably what was observed was not related to Tamoxifen.

Again, this is Dr. Oktay's slide. And his conclusion is that Tamoxifen does not cause premature ovarian failure, and I believe that's absolutely true.

Another point is, though - an important caveat - is that one has to remember that every patient who received care of chemotherapy might experience early menopause. And if they don't, they might have a rise in FSH level. So those things must be looked at.
The return of menstruation does not mean that a woman is absolutely normal. She may have a period for a period of time and still lose it early. So it's important to remember that. It's also important to remember that fertility preservation and pregnancy must be considered in all those women - at least as far as what we want to achieve in those women who regain menstrual function - and that's what we're talking about primarily today.

It's a myth to believe that Tamoxifen causes menopause. And the other thing that I want to emphasize is the GnRHa analogs – Lupron, Zoladex, other things – they said that they might protect against menopause. And I want to do this very quickly, but just to mention - that because younger women, children, who receive chemotherapy, are less likely to develop ovarian failure, it has been thought that since they don't have active ovarian function, it is a protective mechanism, and therefore chemotherapy does not destroy their follicles. That is probably not the case. Because all follicles are chemo-sensitive, and will be destroyed by chemotherapeutic agents.

But the idea behind using GnRHa agonists is to suppress FSH and LH, and to render even a woman of reproductive age, not only amenorrheac, but have an FSH and LH so low that she won't have follicular development. So she will be more like a child who receives chemotherapy than like an adult who has functioning follicle. You can do this either with agonists or antagonists. And it's beyond the scope of this discussion to talk about it. I always use this slide, because again, it's a very pretty slide, but it's very complicated – you could talk about it for an hour.

The point made, with that slide, though, is that all follicles, even when they're tiny and are not developing as they do in the menstrual cycle, are chemo-sensitive and can be destroyed with chemotherapy.

While only the latest stages of follicles are hormone-sensitive, if GnRHa agonists were to be effective, then we would see the prepubertal girls who received chemotherapy would always be fine. But they're not. They actually lose reproductive function.

There's only one randomized study that shows that in fact, there is no benefit, and I won't go into great detail here, but it's by Waxman and al. showing that if women who were treated with GnRHa analogs, four of eight women stop menstruating, and those women - controls - who didn't receive it, 6 out of 9 stop menstruating. Absolutely no difference.

Now, I should tell you, there is an investigator from Israel named Blummenfeld [phonetic] who has shown, in his investigation in Hodgkin's disease and leukemias, that in his hand, using the GnRHa analog to suppress menstrual function may help some of these women. He is the only one and I would like to be corrected if anybody knows of another study. But he is the only one that has shown that indeed there is a difference.

So now I have given you all this preamble about some of the – what happens with chemotherapy, and in other cancers with radiation therapy, what can we really do to preserve reproductive function?

What are the available technologies? Well, egg or embryo freezing. In many cases with cancers, there's not enough time, which is required for ovarian stimulation to get eggs or embryos. Of course, with breast cancer there's a risk of estrogen exposure, so that one would not want to use stimulation. Dr. Oktay will talk about these two options and this is very nice work that he's doing at the Center for Reproductive Medicine here at Cornell.
He will also talk to you about his pioneering work on ovarian tissue freezing and transplantation, where you don't need to wait; you can just freeze ovaries. I won't talk about egg donation and gestational carriers; obviously, these

are well-known to all of you. But if you use this, of course, it means that your own ovaries no longer function and this is, of course, available to all people who accept this type of treatment.

Now, who are candidates for pre-treatment? That is, for pre-treatment IVF -- namely, who might freeze their embryos to save the reproductive function? They have to have normal ovarian function; they have to have a partner who's dedicated to freezing embryos. There can be no medical contraindication to elevated estrogen, as we do have in breast cancers. And of course, the oncologist must give us permission and allow us the time to stimulate the woman so we can get the eggs and therefore have embryos or eggs to freeze.

This is a case of a Hodgkin's disease and I just wanted to give you an example of what happens, what we do, in IVF to freeze eggs or embryos. Essentially, we give gonadotropins -- the same follicle-stimulating hormones that every woman has. We give it at a high enough level so that we get estrogen production. Multiple follicles are developed on ultrasound. We retrieve your eggs, we fertilize them, as illustrated here, and then we freeze them.

What is the chance that if you freeze embryos, you will have a baby? This is embryo cryopreservation results from '95 to 2001 at Cornell. And bottom line here, that 80 percent of all the embryos that we freeze survive -- I don't think I need to go over every single number – and that the pregnancy rate per transfer is about 66 percent. Embryos.

In the old days, we froze all embryos; in these cases, in pronuclear stage, right after fertilization. This is a day after the insemination. This is two days after the egg retrieval. This is three days, an eight-cell embryo. And this is five days later, a blastocyst. Almost all the freezing at Cornell now is in the blastocyst stage.

For women with breast cancer, women who cannot be stimulated, we can go get a single follicle, get a single egg, inseminate the egg, get the embryo, and let it go through these stages, and if we get a blastocyst, we will freeze the blastocyst. Blastocyst transfer is very, very successful and I'll skip that slide for time's sake.

I will tell you that we have a new method of freezing for blastocysts in the last two years. And the bottom line here is that we have an implantation rate per single embryo of almost 40 percent, and a survival of close to 80 percent, as compared to our old method, where the survival was only 40 percent and the implantation was 17 percent. And we have a pregnancy rate of 64 percent, when we usually put two blastocysts in.

That's relevant, as Dr. Oktay will show you also. If you get one or two eggs and two embryos, and you freeze them, you have a much higher chance to achieve a pregnancy nowadays then you did even three years ago. There have been great improvements in cryopreservation technologies.

Embryo freezing, of course, is clinically proven. But it requires ovarian stimulation. With non-blastocysts, there was a 16 percent implantation rate per embryo; with blastocysts now it's 38 percent. And of course, in case of embryo freezing, one must have a partner or one must use donor sperm.

If you don't have a partner, the only other available thing, if you can stimulate or if you are willing to freeze one egg or at most two eggs, with a natural cycle, you get this mature egg, and you could freeze it.

And I'm not a freezing expert, but who are candidates for cryopreservation? As we mentioned, chemotherapy, radiotherapy candidates who have no partner. And if you have two or four weeks to undergo stimulation and retrieval, of course that's ideal because then you have multiple eggs. And of course, if there are no objections -- if there are objections to embryo freezing, and if somebody wants to avoid the need for egg donation in the future.

The difficulty with egg freezing, it's been very difficult to freeze. It's been very inefficient. This is Dr. Porcu's slide that Dr. Oktay lent me. With freezing of eggs, there is damage to many organelles within the eggs, and hardening of the membrane of the egg, so that fertilization is difficult. And it's been very difficult.

Up to about two years ago, total, in the whole world, there are only 26 babies born from egg freezing. Twenty-six.

Dr. Porcu reported her results in Torino and more recently in Seattle, and I think that I will probably skip this. But just to tell you that she has a 66 percent survival rate of eggs.

And again, to make it short and sweet, pregnancy rate per cycle of 17 percent. 1 in 5 pregnancies wound up as an abortion. But at the recent ASR meeting, we heard some very exciting work about egg freezing, and this is relevant to this group as well. We heard two talks; one from Porcu, from Italy, from Bologna.

She reported that per thawed egg, she had a 3 to 4 percent baby rate. Per egg. While Yang, from Florida, reported a 12 percent baby rate per thawed egg, in their egg donation program. These people – if people can duplicate their work, and certainly we hope that other people will do it – have taken egg freezing maybe two, three, four steps beyond what it was before.

And if this can be proven to be the case – and if we duplicate it – this will revolutionize what we do in terms of preservation of reproductive function. And we can see that it might be reasonable to even, without stimulation, to take one egg or two eggs, and then freeze them in one, two or three cycles, before undertaking chemotherapy or radiation therapy, in certain instances.

But I will say that despite the improvement in success overall, pregnancy rates with egg cryopreservation are still, worldwide, relatively low, and they remain a viable option if embryo freezing is not possible. If there's no other option, one should freeze eggs. If there's an option to freeze an embryo, I still think that success rate is four or five times higher than with freezing oocytes.

So Dr. Oktay, of course, will give you some of the work that he's done in the other areas of preservation. But I would like before I end, in the next two and a half minutes, just to share with you a little bit of work - because Dr. Oktay will talk about ovarian tissue cryopreservation - about some of the work that Dr. Takumi Takeuchi and Dr. Palermo are working, in our laboratory, in an area that we called Oocyte Manufacturing. Or maybe it should be called Oocyte Creation, since Manufacturing does sound somewhat commercial. And I was going to change it because someone in the audience of a lecture that I gave a couple of weeks ago told me that Manufacturing doesn't sound like a good term. But we've used it for a couple of years now.

As I mentioned, why would you want to manufacture eggs? Because some women have no ovaries, at all, or may have exhausted ovarian reserves, meaning that they have very few eggs, and if they do have eggs, if they're older, they may be abnormal.

We know from some early scientific work by several investigators, that if you take immature eggs and you take a mature cell and introduce the nucleus - the 46-chromosome nucleus - into an egg that's immature, that immature egg can induce that mature cell to undergo halving of its chromosomal material, which is what normally occurs when one produces an egg or a sperm in nature.

It's called haploidization. It's a reduction division. Everybody understand that? Or this is too much? The idea is that immature egg cytoplasm - the manufacturing apparatus of the egg - can initiate what we call meiosis of a mature cell from the cheek, from the uterus, from the skin, anywhere. And this work was actually done in 1997 and '98 by these investigators. This is the idea. I'll only present the idea to you.

You take a mature cell from anywhere in the body. It has 46 chromosomes. You introduce the nucleus in an enucleated, immature egg from someone else. You take the chromosomal material out from this egg, and this is what you get.

You take this nucleus; you introduce it into this, and essentially you kind of fool this cell into thinking that it's no longer a mature cell, and reprogram that nucleus so that it can undergo the reduction from 46 chromosomes to 23. You need a 23-chromosome egg and a 23-chromosome sperm to get together to produce an embryo. Okay?

So this is schematically what the idea is. You introduce that mature nucleus into that immature egg. You fuse it together with electric current. Like here. And you remember the egg I showed you before? It had a organelle that it extruded? It's called a [polar] [phonetic] body. Well, this contains 23 chromosomes and this contains 23 chromosomes in the human. And then you can fertilize it with a 23-chromosome sperm. This is what is done.

Immature egg, donated egg. You remove the chromosomal material. You introduce the mature nucleus. This is nuclear transfer technology. Like cloning, but it's not cloning, okay? Cloning endeavors to basically duplicate an

individual. We are endeavoring to basically create a new egg. You fuse them together, and then this extrudes the polar body.

When this was done in an experiment, where we took human mature cells and put them into immature mice egg cytoplasm, either doing mouse-to-mouse or human-to-mouse, we were able to get a 60 percent egg production or polar body extrusion in the human endometrium, and 40 percent using a mouse cell with an immature mouse egg.

Is that clear, or am I confusing all of you? This is a manufactured mouse egg. This is the polar body. And this is the other half of the chromosomes within the egg. This is a stain that looks at the egg.

This is another slide showing both the spindle and the chromosomes in the polar body, right here, and -- since this is green, you're not going to be able to see it, but right here, you can see the chromosomes and the spindle.

And when we send these eggs to Johns Hopkins to be examined from a [soma lead] [phonetic], even in the experiment when we used a human mature cell, and put it into the immature mouse eggs, we were able to show that it was divided in half, because there were 23 chromosomes, as illustrated here, of the human mature cells, divided from 46.

Now, I will tell you that Dr. Takeuchi and Dr. Palermo's work is continuing and they have done this in the human as well, not for clinical reasons, but to see if it's possible in terms of experimental. But we could say that in the mouse, we're able to use immature eggs to create, to haploidize, or create, the new egg.

Now, can humans do this? And I'll show you very quickly. If you take a human egg, remove its chromosomal material, and take a mature cell, like this one, pick it up with a needle, put it back into that egg -- with the chromosomal material was removed from that egg – the donated egg, put it together; you're able to halve the chromosomes. And you see two packets of 23 chromosomes each.

In mice, you can fertilize these, and they will extrude, after you introduce the sperm, they'll extrude the extra 23 chromosomes. And while I won't show you results, we've actually had blastocysts – 5-day-old embryos – produced in mice. But no live born.

When we look at this genetically and look to see if this indeed, these cells, these new created vesicles are normal, then we can see that by using a stain for these chromosomes specifically for various chromosomes, that they contain one set of chromosomes, not the usual two sets, that you see in mature cells. As illustrated in this particular slide. Fifty percent of all these eggs that we try to produce are actually normal in terms of halving the chromosomes.

So, why did I share this with you? In my view, this is perhaps the most exciting theoretical work that I've seen in our field in many, many years. Should it work – and it may work with a very, very low efficiency when, indeed it does – it will revolutionize our ability to treat infertility.

Dr. Takeuchi showed that you can do this not just for women – in terms of producing new eggs – but that you could also use it to produce new sperm. So just imagine, anybody that has a normal cell anywhere in their body, by using someone else's egg, introducing that mature cell into an egg, that egg will direct that mature cell. It will basically reprogram it, to create a new gamete.

We certainly believe that further genetic assessment on manufactured eggs must be carried out. It should not be applied to the human until we know that we have live born pups in other animals and they are healthy and they're genetically normal. So by no means are we saying that this is ready for prime time. It is not. But it is extremely exciting.

Although this is a procedure that is technically similar to cloning, in terms of nuclear transfer, it ensures that you have two parents, a sperm and an egg. We think that somatic cell hyploidization, or egg creation, or sperm creation, may become a viable alternative source of eggs, not only for age-related infertility, but will provide a chance for patients with exhausted ovarian reserve, absent gonads, or people that lose their ovarian function because of chemotherapy, or any other cancer treatment.

So. I use a slide that almost I used the other day. What about preserving reproductive function in the face of breast cancer? Where are we going to be in the future? Certainly, embryo freezing, blastocysts, is here. It works. Highly efficient nowadays. Efficiency has improved in the last two years. Egg freezing appears to be promising. Time will tell if all of us can duplicate the people in Florida.

Ovarian tissue freezing – Dr. Okay will share with you some of his fantastic work. Egg manufacturing – only time will tell.

At the end of the day, I think we should all be grateful that we've had some tremendous strides in medicine. We wouldn't be here today if cancer treatment would not have improved as it did over the last two decades. We wouldn't be talking about reproduction in cancer patients. We wouldn't be talking about preserving reproductive function. In the cancer area, we've seen great strides.

We are beginning to see a glimpse of a tremendous, tremendous revolution in assisted reproductive technology that not only will help the infertility population, but will make it possible for all patients, men and women – people that lose their reproductive function in the face of cancer therapy – to be parents.

And I think Dr. Oktay, in his next talk, will actually continue this exciting odyssey. Thank you very much.

Before I finish, I always forget some slide – I always should show it first. All the work that I presented today is really the work of a lot of people at the Center For Reproductive Medicine and Infertility, or what we call now the Institute for Reproductive Medicine. And I shared with you work by Dr. Palermo and Dr. Takeuchi. And Dr. Oktay of course, will present his work to you.

But of course, all these individuals, who [indiscernible], who created a new media for blastocysts and works on the embryo freezing and so on – all these people, are of course very important in basically making this work progress and develop. Thank you very much.

III. Fertility Options Before During and After Breast Cancer

LINDSAY NOHR: Thank you, Dr. Rosenwaks. And while they're setting up, I'll introduce our next speaker, Dr. Oktay.

Dr. Oktay is an internationally recognized specialist in reproductive endocrinology and infertility, practicing here at Cornell. He pioneered ovarian tissue cryopreservation and transplantation, and performed the first ovarian transplant in the world. Dr. Oktay has also developed special ovarian stimulation protocols specifically for breast cancer patients. He's now dedicated a majority of his research and clinical practices to reproductive needs of cancer patients. So please welcome Dr. Oktay.

DR. KUTLUK OKTAY: Tonight I'm sandwiched in between two excellent speakers, so I'm sort of the pause in between two excellent talks.

It was back in 1995 when we started some of this work in England. Let me correct myself. I went to work with a pioneer researcher, Roger Goslun, in England, because I was interested in this topic. And when we started working on this subject, they all thought we came from space, because there were so few patients who would benefit from this, why to bother with such a subject?

I should say that at the last meeting of the American Society For Reproductive Medicine, this was one of the main topics in the entire meeting. With the help of patient organizations, volunteers like you, we also launched a special interest group, specifically focused on fertility preservation in cancer patients. Many cancer societies are now interested in this topic.

Now, I might have given Dr. Rosenwaks a few cheap slides, maybe, but he gave me the most important thing that I cannot pay back, which is encouragement despite all the odds. And some of the work that we're going to present here wouldn't be possible without his support and encouragement. And also, wouldn't be possible without the support and encouragement of you, and thank you.

What I'm going to talk about tonight, is - following Dr. Rosenwaks' wonderful introduction - several options now emerging to help cancer patients preserve fertility. I'm going to talk about several approaches which I have been developing in the past four or five years.

We have been talking about several subjects and which the introduction was made by Dr. Rosenwaks, so it's going to be much easier for me. To not to steal more time; I'm going to make up for this lost time.

These are the numbers in the United States alone. Approximately 200,000 women are diagnosed with breast cancer. If you look at the age, about 25 percent of those are premenopausal women. And about 15 percent – that's about 20,000 – are under age 45. So reproductive age group.

And with the adjuvant chemotherapy – this is not my expertise, but it's common knowledge to me, now, that survival is significantly improved. But there's a price to pay, and Dr. Rosenwaks showed you this data.

But depending on which regimen you're using, there is a significant chance of immediately becoming menopausal. But most of these who didn't immediately become menopausal will suffer from premature ovarian failure. So everybody's affected; nobody is safe from chemotherapy. Maybe I shouldn't talk like that with an oncologist present, in terms of infertility.

So what I'm going to talk about is a technique that we developed -- ovarian tissue freezing and transplantation; embryo freezing, using these specific protocols, because breast cancer is a specific case. You can't just give fertility drugs and stimulate estrogen levels and risk cancer recurrence or aggravation. We're not going to talk about this, as Dr. Rosenwaks stated, that's the final option.

But why ovarian tissue freezing? In this procedure, you wouldn't need the stimulation, so that you wouldn't have that risk in breast cancer. And you could do it any time during the cycle, so if there was a rush, you didn't have to arrange things - time, and all that.

And you can not only restore fertility, because you're putting the ovary back; you can also reverse menopause. And it may be an issue with breast cancer patients. However, you do require surgery to have the ovary removed. And I've found, over several years, that for many breast cancer patients, this is just an added burden, because they're already undergoing surgery. But some patients do choose this.

So how is ovarian tissue frozen? And I should have another slide, but this was a very young patient, it wasn't a breast cancer patient; it was a 10-year-old, as a matter of fact.
But the main idea is to collect the skin of the ovary, which contains all these young immature eggs, and you have to cut them in tiny pieces, so that you can fit them in these little bottles that can fit into the freezer, that is computer programmed, so you'll be able to fit them in there. And they're put in these specific anti-freeze substances. Because you can't just plunge tissue into liquid nitrogen; it would be damaged. You have to treat them with anti-freeze substances.

And the main idea is, that these are human eggs, immature eggs, and they range in size and shape, but this is the youngest stage, we call primordial. They're tiny, tiny – 1/200th of a millimeter – 1/20th of a millimeter – primordial egg, it's called. And when you're freezing, you're really freezing these tiny young eggs, which it takes maybe three months in the body to grow, to produce hormones. That's the main idea.

Well, this is the main slide that I want to show you.

Freezing tissue is not that difficult. We get these primordial eggs and put them on ice, but the idea is, how do you get a baby like this – of course, you need a dad for this. And how do you get a healthy baby like that? Debatable. Cheeks, right?

Well, we approach this in two different ways. We can put the ovarian tissue where it came from, in the pelvis, in a natural situation. Or you can put it in somewhere else, easy to put, easy to take out. And let's discuss these.

We reported that this first approach, putting it in the pelvis, sometime ago. Because you're chopping up these ovaries into tiny pieces, now you have to put them back together, if you transplant it, and that's what we do. This is done orthoscopically, without cutting the belly open, so you have to put them together and make a little frame. So this is what's done. It's an absorbable frame here. And then get it in orthoscopically through these ports. And suture them in the pelvic side wall. Very meticulous.

And this is the first patient who we did the procedure, and I don't expect you to solve this, but these are – this ultrasound shows an ovulated egg, this patient ovulated and produced some hormones. Later, in England, they repeated this procedure on a Hodgkin's patient. They also had ovarian function. For a brief period, but this patient had received several chemotherapies prior to freezing, so her ovarian material wasn't rich with eggs. So that explained why she had the short ovarian function.

But we said, can we make this more simple and more practical? And decided that perhaps forearm is a good site to transplant on. Now, why did I do that? First of all, surgeons have been transplanting this tiny gland attached to the thyroid for very many years, in the arm. It works well, so why not to do that? Also, you can do this under local anesthesia, and if there's a problem – especially with breast cancer patients – if there's a need to remove ovarian tissue - this could be practical.

And I'll show you; you can collect eggs from this site. So we did that, with several patients, and I don't want to show you many bloody slides here, but this is the idea. Of putting these like Norplant in the forearm.

And we published this in The New York Times, scientific journal.

Just to give you an idea – short clip – these are ovarian strips going in the arm like Norplant. And this particular patient came several months later, and she had a little lump in the arm, was going up and down. So what do we do? We do ultrasound. And we see eggs. You see this is her skin and there's an egg here; you can see arm muscle.

So we have an ovary functioning underneath the skin. So then we went ahead and collected eggs from that arm, and we were able to get at least one relatively healthy egg and try to fertilize it, which did not succeed.

We did this on another patient, and 25 months later, this patient is still having function with egg development in the arm. And this is just the clip and we show just how it looks in real life. It's a little choppy, but you're going to see it now. It's a little lumpy. It's not that visible if you put it here, even though mid cycle, it can get a little larger. This little lump here is a growing egg beneath the skin.

And again, if you do ultrasound, you can see the egg growing there; that dark circle that has fluid in it. It grows and it sort of ovulates beneath the skin.

So, in summary, you can freeze ovarian tissue. You can transplant it in the body, and you can get egg development. Even though in animals, there have been pregnancies; still, we haven't tried pregnancy - with an ideal patient, I should say. So this is right now where the state of the research is.

Now, the second approach would be freezing embryos or oocytes. I'm not going to get into the details of oocyte freezing and Dr. Rosenwaks has shown you elegantly what the pregnancy success rates with frozen embryos are. But he also told you that if you want to freeze an embryo, then you would need ovarian stimulation; you need to receive injectable medications for 10 days, 12 days, which should raise your estrogen levels.
And this is what happens when you give all these drugs – and this line is your estrogen level – and you would have one rise in estrogen, and then a second one into these drugs. And the fear is that, in breast cancer patients, this would cause problems, so most people wouldn't want to do that.

You could just collect one egg without stimulating; in many cases, you don't get anything, or if you get anything, you just have one embryo. The more embryos you have, the higher the pregnancy success rates in the future. So is there a safe IVF for -- in vitro fertilization, or fertility treatment, for breast cancer patients?

To answer that, we resorted to a drug that's well-known by breast cancer patients, which is Tamoxifen. But Tamoxifen was invented as a birth control pill, not a cancer pill. Then it was discovered that it actually helps women ovulate. There are certain women who don't ovulate regularly, and it was found that it helps them ovulate. And then it was discovered that it was a good cancer drug.

So we said, why not use that to our advantage? So we started giving Tamoxifen for five, six, seven, eight days, just to stimulate, so we can collect more eggs. Because in a normal cycle we have one egg, but if you stimulate them, you can get more.

Now, what Tamoxifen does is, while it's stimulating, it's also protecting breast. So that the breast tissue cannot see estrogen; cannot be stimulated with it. And what some of our patients, after doing this, they have to go on Tamoxifen anyway, long term. And after that, eggs are collected and fertilized and frozen at this stage, but as Dr. Rosenwaks said, that would now go into a later stage.

And I know I have several of you here who participated in this, and I thank you again, and you may have recognized yourself on this table. And I don't mean to reduce you to numbers; I really appreciate your contribution to this study. But this shows all the patients who were in this study.

And there were 12 patients, and some patients did more cycles, because in breast cancer chemotherapy, many of you do know, from surgery to chemotherapy you have six weeks. So you can squeeze in one to two cycles of IVF. And some of our patients are able to do multiple cycles.

So, twelve patients, and ages, what kind of treatment they received after mastectomy, and that's what's shown in the slide. And we also went back and looked at those patients who only did natural cycle, and these are these here. So two patients did both, so we were able to compare them.

A summary slide that – that's the study. If you compare how many embryos you were able to generate in Tamoxifin-treated patients versus who didn't receive any treatment, then you can see that we increased embryo yield more than 2½ times.

Another advantage of this Tamoxifen protocol is that when people used natural cycle IVF, many cycles got canceled. In Tamoxifen group, every single patient was able to freeze at least an embryo, whereas in natural cycle, three out of five patients were able to freeze an embryo. So every patient was able to have an embryo frozen, to be used in the future.

We had several pregnancies. We had certain patients who had breast cancer history, who were not allowed to use fertility drugs, but who had infertility problems, so in those, we used this to treat their infertility and transfer the embryos fresh. So these are the patients who are cured from breast cancer.

And so far, we have two pregnancies and there was one set of twins that was delivered recently, and this was the first pregnancy, delivery, from Tamoxifen-stimulated breast cancer patient with IVF. However, because this study is new, all patients who had frozen, and none of the patients who had frozen embryos had time to come back yet. So in the next two, three, four years, we are counting on you to come back, so that we see how well we did.

We also looked at - to see if Tamoxifen stimulation did any difference in terms of recurrence, short-term recurrence, of disease, and compared it to non-stimulated patients, and so far, nobody has recurrence in that short time. So in the short follow-up, it appears to be safe.

So, in conclusion, you can use Tamoxifen to increase embryo use in breast cancer patients, and you will have less chance of not having any embryos. And it seems that the risk of short-term cancer recurrence is not increased.

Now, some patients did tell us that they wanted more embryos. So we looked at another possibility, using these drugs called aromatase inhibitors, which are also now being used in breast cancer. So another two birds with one stone. And these drugs – they block the body's ability to produce estrogen nearly completely.

So we can do a standard stimulation, but give these drugs so they don't make any estrogen but still be able to produce eggs.

And there is some data on this, on non-cancer patients, because they also use this drug to stimulate ovulation. And putting this out there, to show you how it suppresses estrogen production, they compared this to a fertility drug, Clomid and when you gave this drug, Letrozole, which inhibits the body's ability to make estrogen, you can suppress estrogen levels to a quarter of what it would normally be.

And again, the amount of estrogen made from each egg is also suppressed to a quarter of what it's supposed to. So it's a 75 percent suppression. So this is one of the newer protocols that we are studying. And if you give this, instead of having these big peaks, you can straighten this out so we can do a relatively safe IVF. And obviously, it's a very new protocol and we'll have to see if this would be feasible.

So in summary, that is a very promising protocol.

What about single patients? Dr. Rosenwaks talked about this. You can freeze an egg and the odds are constantly improving.

Are those babies healthy? There are very few of the pregnancies that are reported in the published literature, but based on 29 babies that are followed, born after freezing eggs, only one had an abnormality, and even though numbers are small, this appears to be a normal frequency.

Also, a renowned investigator from Italy, [Eleanora] [phonetic] Purcu, looked at how healthy those babies are. And this shows their apgar score, I'm sure you're familiar; it goes from 1 to 10. And 8, 9, 10 - they're all good, so on average they're all good. And their weights were normal, 2800 grams, and their lengths were good. Most of them are delivered by Cesarean section, but not because of any problems; it's usually because of things, [idea of] [phonetic] the mother.

They were born at the right time. Interesting, there were more female babies – girls than boys. I don't know if that means anything.

So, in conclusion, there are now numerous options available for breast cancer patients to preserve fertility. And this shouldn't be an issue that is overlooked. No fertility specialist, no oncologist, should overlook this possibility. An ovarian transplant patient can restore ovarian function; we still need to see if we can establish pregnancies.

Tamoxifen IVF has already resulted in pregnancies, and it is a promising protocol, as well as using aromatase inhibitor drugs. And the success rates with oocyte egg freezing is constantly improving.

I want to show the slide – the group that supported me with this work. And thank you for your time.

IV. The Effects of Tamoxifen on Fertility

ROCHELLE SHORETZ: It is with great pleasure that I introduce Dr. Ruth Oratz, our next speaker.

Dr. Oratz is an Associate Professor of clinical medicine at the N.Y. School of Medicine, and a practicing oncologist at New York University Hospital. Her practice focuses on breast and gynecological cancers. She also treats women at risk, those with family histories that make them susceptible to cancer, or who have pre-malignant conditions.
We're fortunate to have Dr. Oratz as a member of Sharsheret's Medical Advisory Board. A Sharsheret caller recently described her to me as "the only doctor who cared not only about my cancer, but about my life." Dr. Oratz.

DR. RUTH ORATZ: Good evening. You're getting a lot of biology tonight, and I'm very impressed that you're really able to stick out all this intense scientific stuff, but this is very exciting and very promising research.

And I think that, as we've learned from these last two lectures, there is really a future for preserving ovarian function in our young patients who we're treating with breast cancer.
And let me also reiterate that our goal in treating breast cancer is to cure breast cancer. So that we're doing this work together. We need to cure the cancer and to make your lives fruitful and productive. And that's what this really is all about.

Let me, before I go into some of the details, also reiterate that pregnancy is safe after a diagnosis of breast cancer. And that's something that we have to say at the very beginning of this talk. That pregnancy does not increase the risk of recurrence from breast cancer. It does not increase the risk of metastasis from breast cancer; and it doesn't cause new breast cancers to develop.

We have a very large literature that's published that supports this. Most of the studies, of course, are retrospective, and it's very difficult to get the denominator, if you will.
We don't know how many young women try to get pregnant after they've been treated for breast cancer, but we do know that there are several thousand reported cases in the literature of normal pregnancies, of healthy babies, and this is really a goal that is a realistic and an optimistic goal for us.

We also have heard that there are a lot of factors that go into the creation of a healthy baby. We're focusing a great deal tonight on ovarian function and on the ability to preserve healthy eggs, but there are many, many factors that go into the decision to become a parent and then ultimately into achieving a successful pregnancy.

I was asked to focus tonight, in talking about the effects of hormonal therapy, specifically. And I'm not going to go into a lot of detail on chemotherapy, but during the question and answer period, if you have specific questions about chemotherapy, we can address that as well.

[Technical comment, not transcribed]

You've heard a lot of these terms already, and I just want to make sure you really understand the basic definitions.

What we're talking about with these eggs are the primary eggs – the sort of very small follicles that are present. The eggs are all there at the time of birth. And the average woman has 200,000 eggs more or less when she's born. But those eggs are asleep. They're in a resting state. And it's only at the time of puberty that the eggs will begin to wake up and to develop and, as you heard in the previous talks, to go through that division, to go through that active cycle, where they go from the 46 chromosomes to the 23 chromosomes, and mature into the mature egg.

So one of the problems is that just with time, the number of eggs drops. And again, you saw that slide. So that by age 50, or by the time of menopause, we've gone from 200,000 eggs down to about 400. So age is a very, very important factor in maintaining fertility.

Now, when we think about breast cancer - you know, we've been lumping all of this together and just talking about breast cancer as a single disease – but all of you know that breast cancer comes in lots of different varieties. And it's really not just one disease.

We know that there are many influences that lead to the development of breast cancer and that influence the treatments that we're going to use for breast cancer. But one thing for sure is that breast cancer is a disease that lives in this hormonal milieu. It has to do with our hormones.

We know that the age of menarche - the earlier a girl reaches puberty, the sooner her body starts producing higher levels of estrogen – may increase the risk of breast cancer. Later age of menopause. Whether or not there have been any pregnancies or no pregnancies may affect the incidence of breast cancer.

If there's normal pregnancy, at what age did that first pregnancy occur? And whether or not exposure to exogenous hormones for long periods of time - long-term use of hormone replacement therapy, of oral contraceptives – may or may not have an impact on the incidence of breast cancer.

Because breast cancer arises in this sort of hormonal milieu, hormonal therapy is a very important component of treating breast cancer. In this context, we're also talking about fertility and what is the hormonal milieu of fertility. How can we measure whether or not someone is fertile?

Well, we can't every month slice you open and count how many eggs there are. So we use, as a marker, menstrual function. If you have a normal menstrual cycle and are having a normal period every month, we use that as a probable indicator that you're ovulating and are going to retain fertility.

Whether or not that's the best way to measure fertility remains to be seen. And as we heard earlier, perhaps we should be looking at other measures of fertility – measuring hormone levels or trying to get a better handle on what's going on.

So even if someone has irregular periods following treatment for breast cancer, that doesn't necessarily mean that she's completely infertile. And we know that even young women who've never had breast cancer or chemo or Tamoxifen may have irregular menstrual cycles and may still be able to become pregnant, may still be fertile. So it's a marker, but it's not a perfect marker.

We also know that many, many women – and you saw the indication, the numbers of women who will develop true ovarian failure after chemotherapy. But we also know that a lot of women who have an interruption in their menstrual function – what we call amenorrhea or a period of time with no periods, with no menstrual cycle – that that's temporary. And that for many of those women, the menstrual cycle will resume eight months, six months, twelve months after the treatment is completed.

Now, they may not return to their full fertility potential, but they still may have enough fertility potential that a normal, healthy pregnancy could result.

So, again, when we look back at the literature, it's very difficult for us to really determine how many women retained fertility or lost fertility. We can use this measure of, did their menses resume or did they not?

And we have to probably get a little bit better, prospectively, in all of our clinical trials, when we're enrolling young women in these studies, to ask the question, to collect the data, and to follow our patients prospectively and also encourage them to participate in some of these very important fertility-preserving protocols.

Let me also emphasize that, as I said before, our goal in treating breast cancer is cure. Chemotherapy and hormonal therapy have a very, very important role in treating pre-menopausal women. In pre-menopausal women, more than half of the breast cancers that we see will be positive for the estrogen or progesterone receptor. So a lot of cancers in young women are hormonally responsive.

Because of that, we use hormonal treatment. And this slide is a lot like the slide that Dr. Rosenwaks showed you, where we have this connection between the pituitary gland in the base of the brain, as it speaks to the ovary. And

here, the message is being sent, as we learned, by the FSH, to stimulate the ovary, to produce more estrogen and progesterone.

In post-menopausal women, where the ovary is much less active, we still have estrogen production, predominately from the adrenal gland, and predominately under the direction of the enzyme that you just heard about, aromatase.

So our hormonal therapies for breast cancer are aimed at interrupting these various pathways either of hormone production or of the activity of the hormone on the breast tissue. So what are those hormonal treatments, and how will they impact on fertility for young women?

Well, we know that hormonal therapy is very important; that it prolongs disease-free and overall survival; that it's often used in combination with chemotherapy, and these are the hormonal treatments that we use in young women. In this country, it's rare for us to remove the ovaries as part of treatment. In Europe it still is done a little bit more frequently.

There are other reasons why a patient may consider to have her ovaries removed, but not necessarily for treatment of her breast cancer. That may be more of a prevention question and might come later on. So this is something that doesn't happen too much in the United States, but I did want to bring it up.

We use Tamoxifen as our mainstay of treatment in premenopausal women, and of course now, we're seeing more and more use of the LH/RH agonists, like Zoladex and Lupron. So let's go through these one by one.

We know that any treatment we use for breast cancer can affect ovarian function; it's related to age, which treatment we've used, and for how long you've been exposed to that treatment.

If we remove the ovaries surgically, we remove the ovaries, and you're not going to have normal ovarian function. So then we would need to look at some of these other kinds of techniques, with egg donation, adoption and so on, for future child-bearing and parenting. So there's not much we can do if we remove the ovaries surgically.

Let's talk about Tamoxifen. Tamoxifen is the drug that is most commonly used as hormonal therapy in premenopausal women. This drug has been around for a really long time. We know that it works in treating metastatic disease, and we know that it's very important for adjuvant therapy.

And more and more, we're starting to use it for prevention, for women at high risk. Because they've either had a biopsy of the breast that shows atypical tissue that's putting them at risk for breast cancer, or perhaps because of a genetic risk. So we're seeing a larger number of women who will have been exposed to Tamoxifen as part of their treatment.

It's a great drug. It reduces the incidence of breast cancer by almost 50 percent. It reduces recurrence rates and death rates after the diagnosis of breast cancer, and very importantly, prevents the development of new cancers in the opposite breast.

We have a lot of information about Tamoxifen. It's been around for a very, very long time. In one of the most recent 1998 overview conferences, we looked at clinical trials in which 37,000 women were randomized in more than 55 trials.

That's a lot of people participating in clinical trials worldwide. In every group of patients whose cancers were estrogen-receptor positive, there was a benefit to taking Tamoxifen – whether they were premenopausal or postmenopausal, node positive or node negative. Every single group benefited from Tamoxifen. Many of these patients also took chemotherapy. But there was definitely a benefit from adding Tamoxifen.

The optimum duration of treatment is five years. But we know that even with one year of treatment there is benefit, and with two years of treatment there is benefit.

It seems like the maximum benefit comes from five years of therapy, and you don't need more than five years. There's no additional benefit beyond five years. So bear that in mind, because we're going to talk a little bit about duration of therapy and the timing of Tamoxifen therapy with respect to pregnancy.

We've heard, I think – and again, this is a very important myth to dispel, and I'm glad that we all agree on this point – Tamoxifen itself doesn't cause the ovary to function poorly. In fact, it stimulates the ovary. It is a fertility drug; it stimulates ovulation.

The chemical structure of Tamoxifen looks a lot like Clomid and I even have a picture of that – that's my one fancy picture. Here it is. I'm very proud of it. Here's Tamoxifen. And here's Clomid.

And you can see there's only one difference in the way this molecule looks, and it's really where this chloride comes off at the bottom of this ring structure. Here's estrogen. And here are some of the drugs that we use in treating breast cancer. So these two drugs are almost identical. And they're going to bind that estrogen receptor and stimulate ovulation in the ovary.

So what happens while you're taking Tamoxifen? Well, you're taking Tamoxifen and we're stimulating ovulation, and lots of eggs are going to develop. And the longer you stay on the drug, the more the number of eggs are going to mature. So it's not so much that Tamoxifen is destroying eggs; it's not. It's not damaging eggs, the way that the chemotherapy can. But if you will, you're kind of using them up during that whole period of time.

You're shaking your head - I'm saying something wrong. Say it correctly, because I – but it's that the longer you stay on it – if you're on this drug for five years, and you continue to ovulate and ovulate and ovulate, at the end of that five years, you'll have fewer eggs. No?

Well, correct it now; I don't want to have – is that too simplistic?

So even this, you won't lose more eggs. Okay, good news. You won't lose more eggs. I'm corrected.

DR. KUTLUK OKTAY: That's one of the fallacies – not fallacy, but one of the most frequently asked questions – even in patients who go through fertility treatment, “If I go through stimulation with the gonadotropins, and I give twenty eggs, and thirty eggs, will that then mean that I [enter] earlier menopause?” But the fact is, that every month that a woman goes through life, she loses about a thousand eggs. As you say, you start to –

DR. RUTH ORATZ: So it's only which number will come to maturity --

DR. KUTLUK OKTAY: [Indiscernible].

DR. RUTH ORATZ: Okay. So it's just a time factor, and it's not the Tamoxifen. Okay.

DR. KUTLUK OKTAY: [Indiscernible] would normally be lost; it's like bringing them [indiscernible]--

DR. RUTH ORATZ: Okay. So it's the same number that you would lose anyway; it's not a bigger number.

DR. KUTLUK OKTAY: [Indiscernible]. I actually look at FSH as the – I don't know if I should use this word – rescue. But it is the growth factor that rescues the [indiscernible] follicles from their inevitable demise. You can almost say that eggs are destined to die unless there's FSH to rescue them. How's that?

DR. RUTH ORATZ: That makes sense. So maybe we should – well, we'll come to that.

What about estrogen levels in women who are on Tamoxifen? We don't have a lot of data. Some of us have been looking at these levels anecdotally. There's one very small published study from Dr. Jordan in women taking Tamoxifen; a little bit of an older group, women in their forties.

All of these women were ovulating and menstruating when they started on their Tamoxifen. They all continued to ovulate and menstruate, and the estrogen levels that he measured in the bloodstream, at least, were the same and

were normal in the women that were taking Tamoxifen. One woman, the levels went up a little bit, and this has to do with this feedback to the pituitary in the FSH.

Now, Tamoxifen has side effects. And these are the incidents of side effects as it's published in the PDR. And you can see that a large number of women will have irregular periods or develop ovarian cysts – this is probably due to this stimulation of the ovary – while they're taking Tamoxifen.

But again, this doesn't necessarily mean that these women are infertile. In fact, we know it's the opposite. You can become pregnant very, very easily while you're taking Tamoxifen. Even if you have some irregularity in the menstrual cycle.

So if you're taking Tamoxifen for treatment of breast cancer, not as part of a fertility protocol, we don't want you to get pregnant while you're on the Tamoxifen.

So the recommendation for patients who are taking Tamoxifen as part of their breast cancer treatment is to use contraception. If there is a decision to go ahead and become pregnant after taking Tamoxifen – and I'm just talking now, again, not about on an IVF protocol, but just in the normal, sort of standard way of taking Tamoxifen - we usually recommend that you stop taking the drug and wait for one or two cycles and then become pregnant afterwards.

And I think this has to do with the safety issues and we don't have long-term safety data on the exposure of fetuses to Tamoxifen, so we wouldn't want that to happen. And we'd want you to be off Tamoxifen when you were becoming pregnant.

Again, the duration of treatment is really the issue, and the age that you are when you start Tamoxifen, because we know the younger you are when you start, the more eggs that you're going to have at the end of it. The older you are when you start and the longer you go, the more eggs you're going to lose along the way.

The combination of chemotherapy and Tamoxifen is a very important one to think about. As we know, chemotherapy actually does damage the eggs, and then if you have chemotherapy, wait some period of time and start Tamoxifen, then you're talking about maybe five, six, six and a half years, of that period of time during which you're having loss of eggs. So there is an issue there about fertility.

Whether or not we can interrupt this five-year Tamoxifen period to have a pregnancy in between are considerations for some of our younger patients. We don't have prospective randomized clinical trials looking at this, but I think that we are all learning - as we're treating our patients, as we see patients with good prognoses, with better outcome from their therapy - that we can be more open-minded and more flexible about some of these considerations for our young patients after breast cancer treatment.

The decisions regarding pregnancy and parenting are very individual and very personal decisions. I think they need to be discussed openly; I think that we need to continue with our research efforts to come up with protocols that are going to be safe for our patients.

At the same time that we recognize that our goal in treatment is cure; and that hormonal therapy and chemotherapy, for now, at least, are the mainstay of treating breast cancer. At the same time that we're doing a lot of research in terms of fertility preservation, our research in breast cancer treatment is leading us more and more to treatments that will be targeted and specific for the cancer cell, and hopefully will be less damaging to other cells in the body, including the oocytes.

V. Support Organizations for Those Coping with Breast Cancer and Fertility

AMY MINES TADELIS: Good evening, everyone, thank you again for coming. I just wanted to introduce our panelists and thank them for joining us tonight. Their input is very important to all of us.

First, Lee Collins. She's here as an infertility patient who has turned herself into an infertility activist. She's a former lawyer, and Lee has now started an infertility consulting practice and is very active with RESOLVE, the national infertility association, where she serves on the National Board as well as the Board of the Massachusetts chapter. Lee has made it her personal goal to empower patients with information they'll need to cope successfully with infertility. Thank you, Lee.

RESOLVE: The National Infertility Association

LEE COLLINS: [Technical comments, not transcribed]

My name is Lee Rubin Collins, and I am a Volunteer Board Member for RESOLVE, the national infertility association. RESOLVE has been in existence for 28 years. We have our national office; we also have more than 50 chapters nationwide. And we provide information, advocacy, and support for folks who are going through infertility.

Now, many people tonight have Power Point. I don't have Power Point. I have peanut butter.

I really could go on and on and on, and tell you about all the services that RESOLVE has for patients, because they are many. But I understand that for women and men who have gone through cancer, there is often a period of time where you go through the cancer treatment, and then it may be years – it may be five years or ten years later – until you're ready to start a family. And that is the time when you will face the challenges of infertility – I hope you won't - but you may face the challenges of infertility and of fertility treatment.

Given that sort of time lag, I thought the most important thing that I could do tonight was to tell you how you will be able to find RESOLVE when you need it. And I thought I would try to do so in a way so that you would remember that RESOLVE is what you're looking for.

So I'm going to show you - and I really mean show you – four key things about RESOLVE. Two of them are about how to find RESOLVE, and two are two key things to know. So, with that, really quickly. Here we go.

First thing, about how to find RESOLVE. What is it? It's the Web. This is the Web; www.resolve.org is our website. Why would you want to go to our website? Well, we have lots and lots of information there.

We have medical information so that you can understand what an infertility workup is going to look like; what the doctor is going to be measuring; what to expect if you're doing *in vitro* fertilization.

We have emotional information; information about the emotional side of infertility, because this is about having babies, and the emotions run very, very deep.

We have resources on the Internet -- physicians to look for, adoption resources, therapists. We have a list of all of our local chapters. We also have bulletin boards that are very active, and you can reach out and meet other people who are fighting the same fight as you. We have chats with physicians through our partnership with WebMD. There is a host of information and support available on the Web.

Second way to find us. The telephone. You should have seen the trouble I had getting this through security - at Logan airport, I should say. The telephone. It was tough explaining why I had an unconnected telephone.

We have a toll-free number. The toll-free number is 888-623-0744. I tried to see if there was a word that could be made from it. The best I could come up with was [NAD ZERO KIDS] [indiscernible], just don't remember that.

Why would you want our telephone number? Well, because we have a Help Line. Five days a week and on Monday nights, you can call up and speak to someone with your questions. It can be medical questions; it can be resource questions. It can be an understanding ear. That's what our Help Line is for.

We also have a Wednesday call-in day. Our Medical Information Director, Diane Clapp, on Wednesday afternoons from 1:00 to 4:00, is there to give out free information and advice. And she will brainstorm with you and help you locate resources.

So call us. Oh, and if you call, you can also join RESOLVE; you can do it on the Web, too. And then you can start receiving our great magazine, *Family Building*. I have a bunch of them here with me today. This one also includes an article by the Executive Director of Fertile Hope.

Number three. Something to remember about RESOLVE. I'm so glad this is a small auditorium, because there's hope that this will work.

Support Groups. These are dolls hugging each other, I hope. Look, trying to have a baby in the face of infertility really takes courage. Don't do it alone. Support groups make a difference.

The Mayo Clinic recently published results of a study showing that attending just a matter of just three support groups decreases depression and stress in women and increases optimism in men.

There's also a study out of Harvard suggesting increased pregnancy rates in women who attend support groups. And we've got them throughout the country. Here in New York, I think there is at least one support group every night. One of them is led by Elizabeth [Grill] [phonetic], who is here. Support groups.

And then, the last thing. The peanut butter. It's a little bit of a stretch, but bear with me.
The reason I thought of RESOLVE and peanut butter is because what do you do with peanut butter on bread? You spread it? And with fifty-three chapters, RESOLVE is spread out across the country.

So knowing that five years from now - you know, you can find a great job in Atlanta or meet a marvelous man in Minnesota. You could be anywhere in a time that you need RESOLVE. We are spread out across the country; we spread our information and our support across the country, too.

So now whenever you need us, wherever you need us, we'll be there. Thank you.

AMY MINES TADELIS: Thank you, Lee, for that very entertaining presentation.

Next I'd like to introduce Pamela Madsen. She's the Founder and Executive Director of the American Infertility Association. For more than a decade, she's been internationally renowned as a leading patient advocate for people with infertility. Her experiences with infertility affected her so profoundly that she devoted her life to helping others understand and navigate the struggles of infertility and reproductive disease. Thank you so much for joining us tonight.

The American Infertility Association

PAMELA MADSEN: You know, Lee, I left an early job teaching kindergarten. I would have liked to have had you. You're wonderful.

There's a lot of hope in this room tonight. You're survivors. You're surviving cancer and you will survive medically-induced infertility, I promise.

And the hope in this room reminds me of the hope that we believed in when we founded the American Infertility Association, because we are an organization of hope.

We believe in your futures. We believe in your ability to have a family. And we will help you, along with all the other wonderful support organizations, to navigate yet another road, to find your way home – to health and to your families.

And how do we do that? Well, we do that in a lot of similar ways that you just heard. We have a wonderful interactive website that's moderated every day by adoption experts, by reproductive endocrinologists, and by mental health professionals. We have wonderful weekly online chats, so that no matter how you're feeling, every day you can log on, participate in a chat, or participate online with one of our message boards.

Every single month, no matter where you live in the country, you will receive our wonderful newsletter. And four times a year, you will receive our wonderful quarterly magazine called *In Focus*, which does just what it says: it brings into focus an issue that we think you really care about.

And many of you picked up *In Focus* downstairs when you walked in. And if you didn't get it, stop back and we'll make sure that you get it.

We also have a wonderful toll-free number where you can call and get a physician referral, speak with our Help Line, and just simply get some peer support. Our families don't always come to us exactly when we expect them to come to us, or exactly how we expect them to come to us.

We saw slides about frozen embryos. I remember – and I didn't have cancer – when my doctors told me they were going to transfer a frozen embryo, my frozen embryo, back into my body. And how scary that thought – My God, they're going to freeze my child. And it's going to grow normally inside of me.

He's 10. He's Dr. Rosenwaks' books. He's thinking about being a reproductive endocrinologist. He's not quite sure yet. Either that, or he may be a baseball player.
He's from a cryo-embryo that was stored for nine months before he was stored in me for nine months. They're healthy babies. It sounds really Star Trekkie sometimes. It sounds a little bit scary sometimes. And it's certainly not how you thought you were going to build your babies, your families, when you were playing Barbie dolls.

But life changes. We evolve. You will find your family. Through birth, through your own eggs, through donor eggs, through adoption, through surrogacy. If you want to find your family, I promise you, you'll find your family.

And I hope the American Infertility Association can help you, along with all the other wonderful groups here, to come home.

Thanks for your time.

AMY MINES TADELIS: Thanks, Pamela. Now I wanted to introduce Lindsay Nohr, who you've all seen before. She is the Executive Director and Founder of Fertile Hope.
Lindsay is a two-time cancer survivor whose personal experiences led her to create Fertile Hope. Thank you.

Fertile Hope

LINDSAY NOHR: In the essence of time, I'll definitely keep this short. I just want you all to know that Fertile Hope is out there. We provide information, support and hope to cancer patients facing infertility.

And something I really want to make clear is that there are options before, during and after treatment. So if you're sitting here now, thinking about all of this talk about preserving fertility before treatments, and you're past that, you probably want to know what can you do now. Well, a lot of the options Dr. Rosenwaks and Dr. Oktay talked about can actually be done after treatment, if you are still fertile and are worried about that shortened biological clock that you now have, the onset of early menopause.

So these are all things that, while maybe you didn't do them before, they are things that can be done after treatment. There is a lot of hope afterwards, as well, in terms of having children on your own, donor eggs, donor sperm, and adoption. And Fertile Hope is here to help you navigate through the process. Whether it's find a doctor

or speak to someone who's been through a similar experience, or get access to the most up-to-date studies, so you know what your options are and how it relates to the cancer that you just have, we can help you.

We are the only organization that combines cancer and fertility, and can look at it through your unique eyes in light of what you're dealing with. So, I just want you to know that we're out there.

We also have our 800 number, our website (www.fertilehope.org), and a very comprehensive brochure. Tonight, your are seeing the best of what we do -- educating you.

Thank you for attending.

AMY MINES TADELIS: Thanks, Lindsay. Next I'd like to introduce Rochelle Shoretz. She is the Executive Director and Founder of Sharsheret. You already know who she is, so I'll keep it brief and thank her.

Sharsheret

ROCHELLE SHORETZ: And I'll keep it brief as well. Last summer, at age 28, I was changing into a bathing suit, when I noticed a small sliver of a shadow on my right breast. A quick self-exam revealed a malignant growth that could have gone undetected for years, because women my age are usually not candidates for yearly mammography.

And I remember asking the doctor not, "Why did this happen?" but, "How did this happen?" How did an otherwise healthy young woman develop breast cancer? Before my diagnosis, I didn't know of a single woman under 30 with breast cancer. Grandmothers? Yes. Aunts? Maybe. But young women? Not one.

And I've come to believe that more frightening than living with cancer is believing that you're the only person like you living with cancer.

In the midst of chemotherapy treatments, I founded Sharsheret, which, as Dr. Rosenwaks pointed out, is Hebrew for 'chain' – a national not-for-profit organization linking young Jewish women in their fight against breast cancer.

Sharsheret aims to pair young women newly diagnosed with volunteers who can share their experiences, both personal and medical. Our mission is premised on the notion that oftentimes, women who are diagnosed want to reach out to others who share, not only their diagnoses, but also their life background.

Sharsheret is a forum for addressing the needs unique to young women fighting breast cancer. And those needs are significant. We are dating, marrying, having children, and raising children, or at the very least, trying to. And the course of surgery and treatment we choose now will have effects on our bodies and on our lives for 50, 60, 70 years to come.

Sharsheret is also a forum for addressing the issues of many Jewish women. The role of religion in daily life with cancer. Genetics, and the increased risk of developing cancer for Jewish women of Ashkenazi descent. And community – comforting for some, but for those who prefer privacy or even anonymity, a little confining.

Sharsheret is a one-to-one pairing of women who call in to discuss a whole host of issues, the results of their genetics test, or how to tell their children, as I did, that they will lose their hair to chemotherapy. We aim to pair women who want to discuss these issues and more with each other, in an atmosphere of confidentiality and respect for the individual lifestyles of our varied callers.

Women who call Sharsheret receive a welcome packet, resource information, and a link with whom they are paired to discuss the issues important to them. Callers can share as much or as little information as they're comfortable with, and are asked to describe the concerns that are foremost on their minds.

The links we make are tailored to address those concerns, and callers are free to speak to as many women as they need, under circumstances of confidentiality that they have established. Our outreach is to the entire spectrum of

the Jewish community – Hassidic, Orthodox, Conservative, Reform, unaffiliated. And the need has been overwhelming.
We've received over 600 phone calls and emails at Sharsheret in just nine months, more than 65 from young Jewish women looking for support or calling to offer their support to others.

Our hope is that women who initially call in for support will, over time, become links themselves, adding to the chain of support that is strengthened by common experience.

Thank you.

AMY MINES TADELIS: Thanks, Rochelle. Finally, I'd like to introduce Mrs. Joy Stimmel. Joy is with us tonight; she is a representative for A T.I.M.E., a Torah Infertility Medium of Exchange. She's a Psychiatric Social Worker in the RocklandCounty Department of Mental Health. She has a private practice that specializes in infertility issues, grief, and bereavement groups.

A. T.I.M.E. (A Torah Infertility Medium of Exchange)

JOY STIMMEL: Good evening, everyone, and I really see this as an honor, to be able to stand up here and present to you some of the information about the organization A T.I.M.E.

A T.I.M.E. is an acronym for A Torah Infertility Medium of Exchange. And this organization really grew out of the work that proceeded us by the organizations of the American Infertility Association as well as RESOLVE.

And what A T.I.M.E. does, is we are able to bring a lot of the information that's out there down to the Jewish couple, and helping them through the infertility process.
A T.I.M.E. provides multiple modes of support for couples dealing with infertility; all couples dealing with infertility. And I would like to give you some examples of what A T.I.M.E. has to offer to the community at large.

Number one, we have a quarterly magazine which goes out to members of A T.I.M.E., which is really chock full of information regarding infertility. And since we are also addressing the specific needs of the Jewish community – some of the doctors did allude to that as far as ethical issues that might be presented in infertility treatment - a lot of this is addressed by different rabbis and doctors that work in conjunction with the rabbis dealing with infertility.

A T.I.M.E. also has a Help Line. We have an office that works normal office hours, and we have a Help Line where you can ask to speak with someone who can give you advice and help in regards to infertility.

There is a lending library that is available, and there are also ongoing lectures addressing various topics with the participation of many professionals in the infertility field, and Dr. Rosenwaks has also been involved with presenting for A T.I.M.E. as well.

I personally facilitate support groups. I've been doing this for a number of years now. This has been a wonderful opportunity for me to help reach out to women who have been having difficulty with infertility, working them through the emotional and psychological process that inevitably reaches all of these women.

A T.I.M.E. also has an amazing website. You can go on it; it is www.atime.org.
And finally, let me just mention to you that actually this Sunday, A T.I.M.E. will be presenting "Infertility and the Jewish Couple." This is going to be a conference that will be located at the Brooklyn Marriott this Sunday from starting at about 8:30 in the morning until 3:30 in the afternoon.

There are many, many different workshops and round tables that will be presented by various professionals in the field of infertility, as well as issues addressing the Jewish couple specifically.

We welcome everybody to take a look at our website and take a look at what A T.I.M.E. has to offer. And just a note from Pamela that AIA also provides support groups and in fact, one of the support group leaders is here this evening.

And as Lee mentioned as well, support groups are an amazing, amazing tool for anybody who is dealing with infertility or any type of loss that they may be experiencing.

The power of being with other women and men who are going through the same experience that you are going through has immeasurable, immeasurable benefits. And I've seen it myself, and what's it's done for me personally, as a facilitator of a support group, has also added to my personal life.

I welcome all of you to look into support groups in any arena, in any area of the United States that you live in, and reach out. We're there to help you.

Thank you. Good evening.

VI. Question & Answer Session

ROCHELLE SHORETZ: We'll open up for question and answer now. Some volunteers will be circulating slips of paper in case any questions come up while you're hearing the answers to someone else's questions.

I apologize in advance. We definitely will not be able to get to every personal question, but I welcome you all to join us for the reception following the Q&A period, and feel free to tap the panelists on the shoulder and ask your question then.

Some of the questions that will come up are obviously very personal in nature, very unique to your own circumstances, and those I'm not sure we'll be able to get to. But if I can generalize your question, it will be easier for me to pass it on.

Q: How can Tamoxifen safely be used to stimulate egg production and also not be recommended during pregnancy? It seems like a contradiction.

DR. KUTLUK OKTAY: Seems like this question is for me. Now, in the context that Tamoxifen is used for breast cancer treatment and prophylaxis, it is used a very long time. And it is used constantly. And Tamoxifen is a drug that accumulates in the body; it has a long health life. So the longer you use it, the higher the levels will be.

In ovarian stimulation, it's used briefly and when you're freezing embryos, your embryos are not exposed to Tamoxifen because we collect those eggs and freeze them outside the body.

Having said that, there is a study out there that was done in England, where they took volunteers who were going to undergo tubal ligation - they can do studies like that in England – they stimulated them with Tamoxifen, with high doses, like 80 milligrams. Twice as high as the dose we used. Then *in vitro*, they looked at embryos, how they developed. There was absolutely no problem.

Also, if you look at the kind of literature, what happens to people who take Tamoxifen, it's not as scary as you think, even though that doesn't apply to the protocol we use. For example, there are case reports where women continue to take Tamoxifen all throughout pregnancy – believe it or not, this happened – and in the case of a male, nothing happened. These are anecdotal reports. But there are a couple of reports when the fetus was female, that there were urogenital abnormalities.

So we definitely don't want anybody to get pregnant while they're taking Tamoxifen. But the way it's used in our protocol, is doesn't affect that.

Q: We have a lot of questions coming up to the front, asking very specifically, how long after completing treatment, chemo and radiation, do you recommend waiting, until trying to get pregnant?

DR. RUTH ORATZ: That's a very important question, and I think is a very personal question. As I said, the data tells us that pregnancy is not dangerous after a breast cancer diagnosis. So there's no magic number.

The other issue -- before I answer that question -- that I want to remind you all of, is when we looked at those charts, remember, not everyone who gets chemotherapy and Tamoxifen will be infertile.

If you're very young when you're treated, 20's and early 30's – before age 40 – even before age 35 – there's a very high probably that you will be able to have a normal pregnancy, without IVF, without ovarian tissue freezing, without embryo transplant.

And all of us have a number of patients who we've followed and seen, who have had treatment for breast cancer, had some period of time after they finished their treatment, and then went on to become pregnant spontaneously and have normal pregnancies.

So not everyone who gets chemotherapy is infertile. It's very important to remember that. It's only about 25 percent of women who are under age 40 who will have difficulty with fertility. Over age 40, over age 35, even, the number goes up to – and it's age-related.

So with that said, is there a magic number? Do you have to wait six months, one year, two years? It's very, very individualized, and I think most oncologists, when discussing this with their patients, choose that number based on the prognosis.

We want to make sure you're healthy before you become pregnant. That definition of healthy and how soon someone is willing to have a pregnancy is going to vary from one patient to the next and from one family to the next.

So there's no magic number. For some women, it may be safe to attempt a pregnancy within three to six months after finishing treatment. For other women, it may be more appropriate to wait a year or two and see how things are going.

So again, I think it's a very individual decision. You'll hear around town, a lot of doctors will say a year, or two years. We use those numbers arbitrarily but they are not magic numbers.

DR. KUTLUK OKTAY: I think there's an important point there. Can I make a comment?

Lindsay got up and told us a very important thing, that options are not just before chemotherapy. The options are during and after chemotherapy – mostly after chemotherapy.

Now, when you receive chemotherapy, depending on the age of the person, you have varying numbers of eggs in your ovaries, so that the younger the person, the less likely that there will be an immediate infertility or menopause. But everybody who gets chemotherapy has lost a good chunk of their reserve.

So even though there may not be immediate infertility, almost everybody will suffer from early menopause. So if, after chemotherapy, you're considering delaying pregnancy, then you have to keep that in mind because your time clock might be much different than somebody who did not receive chemo. But some people will conceive during that process. But if you delay it, then there could be a problem. And that's something to bear in mind.

DR. ZEV ROSENWAKS: I have a little bit of a different philosophy. I think one should look at any problem as if the possibilities at the end might be the worst.
Meaning that for most people, with the new chemotherapeutic regimen, they will have function, particularly when they're younger. On the other hand, if you could do something to guarantee – maybe not guarantee, because nothing is guaranteed, but to insure that you have some reserve, then I think that should be done.

It applies to men probably more often than to women, because it's not that easy to get to the ovaries. And you can get sperm and you can freeze sperm and so on. But on the other hand, I think that it's important to remember that there are certain options like freezing eggs in a natural cycle in Tamoxifen and so on, that should be used in case.

I did not show you – I took some slides out because of time - but we have been taking care of patients with malignancies for at least fifteen years, since I started at Cornell. And we have a fairly large experience, not published as yet but probably should be written up, where we have frozen embryos for couples where there was a problem, many of whom became pregnant on their own. Even though they have, in reserve, frozen embryos.

So while it's important to remember that as the technology improves, and as chemotherapeutic regimens improve – they become gentler and gentler and yet more effective, by various combinations and so forth – with careful attention paid to minimizing reproductive damage, it's not insignificant to remember that if you can, or if you do have the option to do something about preserving reproductive function, you should do it beforehand as well.

Q: Do the studies that show that there is no increased risk of breast cancer recurrence for women who become pregnant after breast cancer apply to women diagnosed at all stages?

DR. RUTH ORATZ: Yes. This is irrespective of the stage of diagnosis. What we know, however, is that prognosis is related to stage. So the risk of recurrence increases if a woman presents with a higher stage of disease. If she coincidentally became pregnant along the way, that doesn't change the prognosis.

This is also true, by the way, of women who are diagnosed with breast cancer during a pregnancy. And that sometimes happens also. And again, the prognosis is not necessarily affected by the fact that you were pregnant when your breast cancer developed; it has to do with what the stage of the breast cancer was at the time that it was detected and treated.

DR. ZEV ROSENWAKS: And I think it's very important also for everyone to remember that when a problem like this arises, like a pregnancy, unexpected pregnancy, while someone is pregnant - I mean, while – if you get a diagnosis of a breast cancer while you're pregnant – you should seek advice from people who have a lot of experience with it.

DR. RUTH ORATZ: Right.

DR. ZEV ROSENWAKS: Because there are many people out there who don't see this very often. And they worry because of the theoretical risk. I think if you go to someone who's had a lot of experience with breast cancer, with pregnancy, with treatment and so on, you will get the best advice.

So there are centers around the country and in New York where there are more people who deal with this daily, while in other places it's sort of a rare event. And they will be more likely to interrupt a pregnancy, for example, or not let it go to 36 weeks, because of worry. So it's very important to remember that.

Q: We talked a lot about early menopause. One question that came up is, for a young woman who is treated with chemo and retained her menstrual cycle, how many years earlier than normal should she expect to enter menopause?

DR. ZEV ROSENWAKS: Well, I think that's impossible to actually predict. I think the younger she is, the gentler the chemotherapeutic regimen, the more likely that she'll have as close to normal menopause in terms of the time that it occurs.

I think one can also obtain blood tests, like FSH levels and other things, in the meantime, that one can have at least an index or an idea, of what the ovarian reserve – how many follicles remain in the ovaries - and get some idea of where they are. But I don't think that one can predict that completely in any case.

DR. RUTH ORATZ: But it really is age-related. So a 45- or a 46-year-old woman getting chemotherapy is much more likely to have menopause very soon after that, than a woman who's 30 when she's being treated. So it's very much age-related but again, it's impossible to quantify.

DR. KUTLUK OKTAY: But maybe if you look at Goodwin data, if you look at the difference between these curves – you cannot predict it. There's about fifteen years, on average – it moves about fifteen years. So obviously, if you're 40, you got chemo, normal menopausal age is 50, so you're not going to know that difference.
But it looks like, at least for breast cancer, you cannot predict that.

DR. ZEV ROSENWAKS: But of course that was with the classical regimen CMF, and I think now with the newer regimen, it's less likely that one will have ovarian failures.
So I think it really depends. One has to look at it case by case. Taking the protocol that was used; the age, duration, total dose as we said – as all of us said, actually. I mean, I think that one has to emphasize that.

Q: We've spoken a lot about women tonight. One question that came in, is there any information about the effects of chemo and hormonal therapies on the fertility of men with breast cancer?

DR. KUTLUK OKTAY: That's a very good question. We know the effect of certain chemotherapy drugs on men being treated for Hodgkin's disease and for other malignancies. And we know that the effects are very similar. So

the same applies, I think, with respect to the alkylating agents, Cytoxin in particular, and some of the other drugs reducing fertility.

But we have also seen, for some of our patients, that this is reversible, and of course, for males, as Dr. Rosenwaks said, it is much easier to obtain sperm prior to treatment than to freeze those sperm. I don't know if you have any other comments with respect to that.

DR. ZEV ROSENWAKS: Yes. One thing that was – well, there's no question alkylating agents are the worst culprits as far as destroying testicular spermatogenic function.

But it should be also remembered that even in men that have no sperm after chemotherapy, sometimes one can go to the testes and do testicular biopsies, and in a certain percentage, one can find sperm in the testes and still get pregnancies.

And there was a paper by Chen from here, with Peter [Schlagel] [phonetic] in *Cancer* – I think it was published last year – where we reported that even in men who had had previous biopsies after chemotherapy, where there is no sperm seen in the biopsy, in a quarter of them, one could find sperm if one did a particular biopsy with microsurgery, as Dr. Schlagel does.

So that in some instances it's – what used to be called post-chemotherapy sterility is not truly sterility with the modern technology. So I want us to take it case by case, and if it's possible, of course, with men, if one can preserve sperm, then of course it makes things somewhat theoretical, because frozen sperm these days, with IVF, do as well as fresh sperm.

So I think men have a little bit of an advantage if their physicians, the people that are treating them, make sure that they freeze sperm.

Q: A number of people have passed up the following question: Do cancer treatments cause severe damage to the eggs or increase the risk of an adverse pregnancy? Many write in that they are concerned about birth defects.

DR. RUTH ORATZ: There's no increased risk of birth defects following chemotherapy treatment, as long as the fetus is not exposed to the chemotherapy. So if a woman is pregnant while she is on chemotherapy treatment, certain chemotherapy drugs will cause fetal abnormalities.

However, we have unfortunately experienced using chemotherapy drugs in women who are pregnant. Again, sometimes in women with breast cancer, sometimes women with lymphoma or leukemia or other malignancies where - for whatever variety of individual reasons pertaining to pregnancy and starting treatment, and in the third trimester in particular - it may be safe to use certain drugs that the fetus can be exposed to and will not be born with congenital anomalies.

In the first trimester, it's a little bit trickier. So it depends on the drug and on the point in pregnancy at which the fetus is being exposed. If you have completed the chemotherapy, the drugs are out of your system, there is no risk of fetal anomaly, as far as we know.

DR. KUTLUK OKTAY: Let me take a stab at that. If the question is, can you get pregnant immediately after completing chemotherapy, there's --

DR. RUTH ORATZ: [Indiscernible] fetal anomaly.

DR. KUTLUK OKTAY: Well, safe because, you know, the pregnancy would be abnormal. There is a study in laboratory animals giving them chemotherapy and then looking at fertility, and it shows that within the first six months after chemotherapy there is an increased incidence in anomalies and fetal loss. Because it takes perhaps three to six months, especially in humans, to clear eggs and start producing all these newly developing eggs.

So because of that reason, if you are considering pregnancy, you should wait perhaps six months after the completion of chemotherapy. Not because chemotherapy is in your system, but the damaged eggs are in your system.

DR. ZEV ROSENWAKS: And because I lecture a lot about men and reproductive function as well, I will tell you that in men it's recommended that they wait a year after chemotherapy before trying.

And that's based on looking at the evidence in chromosomal studies that have shown an increased chromosomal abnormalities within a year after chemotherapy. After that, it looks like it's perfectly normal.

DR. RUTH ORATZ: We don't have a lot of data in humans. The data is all retrospective, and it's very variable in terms of how long women have waited.
That magic number of one to two years is the usual waiting time. So that may be why we don't see those reports, because most women are not having pregnancies so soon. So we usually do recommend waiting.

DR. KUTLUK OKTAY: It becomes important when the patient comes after chemotherapy and wants to freeze embryos, for example, immediately after chemotherapy, because they're afraid that they may go into menopause shortly. In which case, we don't do it right away, because those embryos could be damaged. Then it becomes material.

Q: Some doctors seem more concerned with the long-term increase of hormones during pregnancy rather than the short-term increase in hormones during IVF. Any comments?

DR. RUTH ORATZ: I don't know of any carefully collected data on the use of IVF in women after a breast cancer diagnosis. But we certainly have thousands of women who have received IVF treatment. And in those women, we do not see an increased incidence of breast cancer. So the IVF treatment in normal, healthy women does not seem to be inducing or causing breast cancers.

Again, we don't have a big group of women who are breast cancer survivors who have undergone IVF, but I suspect, as we start learning more about the biology of what's happening, that we're going to begin to look at some of these protocols using Tamoxifen, using aromatase inhibitors, and some of the novel agents, and we'll come up with protocols that we are comfortable with as being safe for this population.

DR. ZEV ROSENWAKS: I would say most oncologists would vote against stimulating with IVF in the presence of a breast cancer diagnosis because the estrogens are unopposed; they're 2,000, often, micrograms; very high levels that stay for several days, remain for several days. So our experience has been that the majority would not recommend stimulation. This is what led to the Tamoxifen protocol and now these new agents as well.

The question of pregnancy is an interesting one, because if you look at the data, it's somewhat mixed. And the question is, does estrogen plus progesterone somehow – is it somehow a different environment from a breast point of view? And therefore, is not analogous to the stimulation that occurs in IVF.

I will tell you the there is one study from Australia that suggested that women who received treatment for infertility with ovarian stimulation drugs, within a short period after their stimulation were more often diagnosed with breast cancer than women who did not receive treatment.

However, the long-term follow-up of the two groups was no different. So the incidence of the breast cancer was no different in the treated versus not treated, but it may be that either giving estrogen somehow enhanced the tumors so it was palpable earlier. But certainly not from an incidence point of view; there was no difference in treated versus not treated patients.

DR. KUTLUK OKTAY: My experience with oncologists is that most of them would not approve. And why do we give chemotherapy after a mastectomy? Because breast cancer is a systemic disease, am I right about that? So the cells are still there.

So even after mastectomy, if you go ahead and give the most significant stimulus for the cells, which would be estrogen in high, high doses, you can easily stimulate [at least] [phonetic] in laboratory conditions, this is what happens. And in pregnancy you have all these different hormones opposing each other, and it's a different situation.

DR. RUTH ORATZ: It's a different mix. So physiologic pregnancy is very different than using the hormones one at a time, if you will, in very high doses. And this also relates to the question we have with some of our older patients about the safety of hormone replacement therapy after a diagnosis of breast cancer, and this is also very controversial. It's the same kind of question.

Q: And I think this is a very appropriate question to end on. What is clear from tonight's presentation is that oncologists and fertility specialists must talk to one another. Do they? Is there a forum for this discussion?

DR. KUTLUK OKTAY: Every day.

DR. ZEV ROSENWAKS: Well, I think it's important to emphasize that we don't really practice in a vacuum; that we look to the oncologist to give us advice regarding whatever the malignancy is, I mean, in terms of prognosis, safety.

We can answer what can be done, but we cannot really ultimately decide when and how it should be done. That is up to a team which must, must always, at the head of the team, it must be the oncologist who treats the patients. Because really, safety, at the end of the day, is the most important aspect of what we do.

VII. Closing Remarks

LINDSAY NOHR: Thank you. I'll keep it short and let you be on your way.

Please join us for refreshments outside. Some of the panelists will be upfront and outside, and available to answer your personal questions.

I would like to take a moment to thank everyone. Thank you to our presenters for their time and expertise. Thank you to our sponsors for making this night possible. Thank you to our volunteers for donating their time as well. And, thank you all for attending.

On behalf of Sharsheret and Fertile Hope and all of the presenters, we hope you all walk away feeling empowered with the knowledge you now possess and can move forward making educated personal decisions.

Thank you.

VIII. Disclaimer

The information contained in this document is presented in summary form only and 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 provider. The document does not recommend the self-management of health problems. Information obtained by using the document is not exhaustive and does not cover all diseases, ailments, physical conditions or their treatment. Should you have any health care-related questions, please call or see you're 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.

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