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>> Welcome, everyone, and thank you for joining the series. Our webinar will address Fertility Concerns for the Brain Tumor Survivor presented by Lisa Kulp. All lines during your webinar are muted. If you'd like to ask a question, please type it in the box on the right-hand side of your screen. Dr. Kulp will answer as many questions as possible, and tomorrow you will receive an invitation to complete a survey. We would appreciate it if you would take a few minutes to answer four short questions about today's webinar. We want to know if these are meeting your needs or if there is something else we should be offering. We are recording today's webinar, so if there is someone who cannot attend, they can watch the webinar there. You will be receiving a webinar link in the e-mail, and you can forward that as well. We will pause for a moment and begin our recording here. The American brain tumor soarings is pleased to welcome you back to our webinar series. Today we will discuss Fertility Concerns for the Brain Tumor Survivor. My name is Joian Dimas. I am delighted to introduce our speaker today, Dr. Lisa Kulp. Her research into fertility preservation methods for women who are facing potentially sterilizing cancer treatment. Thank you for joining us, Dr. Kulp. You may now begin your presentation.

>> Thank you for inviting me. This is a subject that is of great interest to me. I would like to talk about fertility concerns for brain tumor survivors. We are going talk about the effects of radiation therapy that impact the hypothalamus and pituitary. I will try to touch on how this relates to men, and much of what I say can be generalized to men. What we know is that cancer chemotherapy -- these therapies can cause damage to the brain in places that regulate the reproductive system. Cancer was nearly almost always a fatal disease. The first goal was cure, the secondary, to avoid overload of awe cute toxicities. They would imbibe one drug with a side effect in different categories. Now survival rates are such that planning for the future is appropriate and long-term toxicities are getting more attention. The American society of clinical oncologists has said that as part of the consent process, oncologists should discuss the possibility with their patients and refer patients to people who can help them with those issues. Sperm and embryo preservation are considered standard practice that should be available to anyone approaching cancer treatment. What we know is that the reproductive control systems are located primarily in the hypothalamus, which is located at the base of the brain between your eyes and above your nose, and in the pituitary, below the hypothalamus and above the roof of the mouth. Because it is in the center of the skull, basically, radiation that treats most any tumor in the brain is going to impact the hypothalamus and pituitary areas. This is kind of a schematic that shows why this is important. The hypothalamus, the part of the base of the brain, releases, for reproductive considerations, GNRH. This hormone travels to the pituitary, below the hypothalamus, a space of a half-inch to an inch, and in response, the pituitary releases LH and FSH. These act on the gonads to make steroid hormones that feedback to the hypothalamus, and the hypothalamus knows what the gonads are doing, and the regulation hormones change in response to the message it gets from the gonads. When this part of the brain is affected by radiation therapy, the regulation of the gonads can be thrown off. I have put a list here of common causes of radiation to this area of the brain in order of decreeing -- tumors in the nose or the pharynx, behind the nose and the roof of the mouth are near this area. These tumors often require high doses of radiation and affect the area in many cases. Pituitary gland tumors, when they are radiated, the pituitary gland is damaged. Brain tumors in general require radiation that is enough to

affect this part of the brain, although the dose is usually less than what we see for nasal tumors or pituitary gland tumors. Patients with leukemia sometimes receive prophylactic treatment of the brain. This is less common now. Whole body radiation occurs in preparation for a bone marrow transplant and is less likely to damage these areas of the brain. What we know is people who have had previous radiation in an area that includes this regular tear system, about 74% will have some amount of thyroid dysfunction. The thyroid is regulated in that part of the brain. About two-thirds will have disif you can of the ovaries or testicles. 52% will have an elevated prolactin hormone, and that can interfere with the function of the ovaries or the testicles and a smaller number will have adrenal dysfunction. So the part of the pituitary that governings the thyroid is most sensitive. The second is the part that regulates the gonads. If these systems fail, you can have hypothyroidism, which is underack Ty thyroid if the gonads are not working, you can fail to go through puberty. People can be diagnosed with growth hormone deficiency, and can have low testosterone and other hormones. We can substitute for those hormones for general well-being. People with symptoms of lowest Jen and low -- low estrogen and testosterone cansupplemented. People can be treated with growth hormone and thyroid hormone is very easy and commonly done. But what about having a baby? I think we should first address, is it safe to have a baby, can I still have a baby, and what can I do before treatment to maximize my chances of being able to have baby after treatment? Is it safe to have a baby after cancer treatment? In general, the answer to this question is yes. There are some tumors that are estrogen-dependent. The level goes high during pregnancy, so that can be a consideration, but those are tumors like breast cancer and not the kind of brain tumors that we're talking about today. What we though from a fair amount of data is the this point is that the offspring of people who are -- have been treated for cancer are usually healthy. This, of course, assumes that there has been a certain amount of time passing after the treatment with cheep chemotherapy or radiation, but after a certain amount of time, let's say a couple of years has gone by, then the previous cancer treatment does not affect the chance of a miscarriage, prematurity, or the risk of birth defects in the babe I why. If a person is ready to try to have a baby after a high dose of radiation to the rain, all of the regular tear hormones that are present can be replaced. Perm production and ovulation can be supported so that natural conception can occur. These treatments are expensive and have a risk of multiple pregnancy, but they are rel Tyly easy to manage. This will be a review of what we're able to replace. This hormone, GNRH, is available in a bottle. Used to be available in this country, not so widely available anymore. But we do have LH and FSH in a bottle that we can provide and administer to make the testes function normally to make sperm and make the ovaries function normally to ovulate and release an egg. Chemo therapy is another problem. This can cause damage that can not be overcome. The younger you are, the more likely you are to recover from the effects of chemotherapy. The dose of the agent is important in terms of how badly it affects the gonads, and the agent is specific. We know some agents like psychofasamide or alkalating agents are especially toxic to sperm and eggs. This can result in loss of eggs and sperm production. Men continue to make sperm all their life, so if the sperm production is not completely wiped out, the sperm production may recover. Women, on the other hand, women have all the eggs they will have when they are born, and loss of eggs -- eggs that are lost cannot be replaced. So let's talk for a minute about the effect of chemotherapy in men. The germinal eppithelium is more protected. Most treatments will result in impaired sperm production. This is damaged more so than the hormone producing tissue. So a man can have impaired sperm production without effects on his testosterone production. So a man can feel healthy and have

normal sexual function even if he no longer makes any sperm. If a man is facing a treatment that is likely to damage his sperm production, we can freeze sperm for him prior to treatment. Surprisingly, when we started treating -- we started offering sperm freezing to men who were facing chemotherapy, we found that many men had abnormally low sperm counts when they were diagnosed with cancer. Some of these men, of course, were quite ill when they were diagnosed, but some were asymptom attic -- freezing sperm leads to about a 50% loss of the ability of the sperm to swim, and about 50% loss of viability. 50% of the sperm do not survive the freezing process. But there are ways with treatment that we can work with even very low numbers of sperm, so it's generally worth freezing sperm prior to treatment. The cost and the time for sperm freezing is not prohibitive. It costs about $400 to store a sperm specimen in Los labs. There is the sharing hope Fram that I will talk more agent later that provides the service at about half price. Most centers have an annual storage fee. We ask you to decide about what happens to your sperm if you do not survive, and ideally, if I man was able to give a sperm specimen every other day for about three times, each of those would be divided up into two or three vials, which might yield with 8 or 10 vials of sperm, which is needed when the time couples to have a baby. For boys younger than puberty, they are more resistant to the effects of radiation because they dod no produce sperm until they reach puberty. There is some work being done in which testicular tissue is frozen and saved with the idea that it can somehow be replaced into the testicle or perhaps sperm can be developed in a laboratory setting in the future to produce sperm for this young man. Currently, there is no technology that is available to use this sperm -- this tissue at this point. We don't know the best way to freeze it. We don't know that the tissue will survive. We are uncertain about how to use this frozen tissue. It is considered quite experimental, but is sometimes offered. Now, let's tern for a minute to the effects of chemotherapy in women. Again, the effects are age, dose, and agent-dependent. Women have all the eggs they are ever going to have when they are borne. Therefore, if a chemotherapy destroyed 90% of a woman's eggs, this will leave her with many more eggs than if she loses 90% of her eggs when she is 40. So younger women are more resistant to the effects of chemo. Alkalating agents are considered to be the worst. With don't know previcely with different chemotherapies which are safe and which are not. In general, we think they all cause some damage. Part of the reason that we don't really know is the combinations that are used change regularly and just when we feel like we have a handle on one combination or another, then the treatment plans change. In general, I tell people that there is a about a 50% chance that all of their eggs will be destroyed as a result of their chemotherapy. Some women, young women or girls have been treated in childhood, and clearly they still have eggs left because many of them will go through puberty and start periods, which indicates they are ovulating and still have eggs left. But if you study these women closely, you can recognize that the of -- -- ovaries are small, and the cysts where the eggs are found are less than women who have nod had cancer treatment. These findings indicate that there has been some loss of eggs, though not obviously all of the eggs are lost. So what can we do for women to try to preserve their fertility prior to treatment? Embryo cryopreservation is a technique. It has been available for 30 years. It's not perfect, but we would have the details of that process pretty well worked out and understand how to do it and can g if you a good idea of what the expect. Oocyte preservation is egg preservation. In this, the egg has not been fertilized, an embryo is a fertilized egg. We can freeze a piece of the ovary with all the microscopic eggs present in that piece of ovary. Let's talk for a second for embryo cryopreservation. It's a well-established technique. You have to go through an invitro fertilization cycle. We have to have a

window of opportunity prior to treatment. It requires a partner because on embryo is a fertilized egg. Approximately 80% of embryos will survive the freezing process for use later. At this point, we are having about a 40% to 60% chance that a pregnancy will occur every time two of these embryos are put back in the uterus after treatment has been completed. If we don't have a male partner and we have to freeze eggs that are unfertilized, this is a newer procedure. It has been, until recently, considered experimental. At this point, they're starting to say it's not, but it still has a much lower success rate. It also requires that you go through an in vitro cycle that can take duoto three weeks, and there is a 3% chance of success, which means a baby with the frozen eggs. To try to understand the difference between embryo and egg freezing, let's say a woman who has 15 eggs obtained at the in vitro fertilization procedure, if you were able to fertilize the 15 eggs, maybe you would get 10-12 that would fertilize properly and continue to develop properly and be available for freezing. If you had 10-12 embryos, that would be 5 or 6 times that you could transfer two embryos each time. Each time you transfer two, there is a 40% of 60% chance of pregnancy. So if a woman was able to get 15 eggs, we would feel very confident that after 5 or 6 embryos with almost a 50/50 chance to get pregnant, we feel confident she would have a baby or two out of those embryos. If we were not able to fertilize the eggs and we have just frozen eggs, maybe 12 would be mature, healthy, viable eggs, and at 3% per egg, we say about a 35%-56% chance that we would get one baby out of that whole batch of eggs. So being able to fertilize the the eggs and create embryos has a much higher success rate, but if there is no male partner, freezing eggs without fertilizing them is a process that is under development. It has a steadily improving success rate, and the people with the best success rate are young women, which are usually or candidates for fertility preservation. If neither egg freezing nor embryo freezing is appropriate, or there is not enough time, we do sometimes freeze a piece of the ovary. The ovary has many eggs in it that are tie any and microscopic. Hidden in the cortex, the outside covering of the ovary. This is experimental. It can be done on very short notice. It doesn't need to delay any cancer treatment. Insurance, for the most part, is not covering it at this point. And there is some discussion in our field about whether it's best to freeze just a piece of the ovary -- ovarian cortex, the covering of the ovary, versus freezing the entire ovary. It's possible you will hear discussion about one or the other if this option is offered to you. If you have a piece of ovary freezing and you're ready to have a baby, what will we do with the tissue? At this point, we are not able to get eggs from the tissue in a laboratory setting. In vitro means a laboratory setting, and the eggs in that piece of ovary are not mature, so they cannot be fertilized. They need to be matured before they can be fertilized. As yet, that is not possible. A lot of work is being done, but we are a long way from creating a baby from a piece of ovary in a laboratory setting. We can take a piece of ovary and put it in an animal. This is not advised. It is being done to understand the best techniques rather than get eggs that would be used. Autologous transplant is being done. There are approximately 18 babies born from ovarian tissue that was frozen and put into the woman at a later date. That may not sound like much, but it is a procedure that is do-able, and is getting a lot of attention and is something that will improve with time. If you have the piece of ovary and you're ready to put it back, there are several things we think about. What is the best timing? How long will that piece of ovary last? What is the best place to transplant that piece of ovary, and is there a risk of getting the cancer back by putting the piece of ovary back? The transplants seem to last 2-3 years, maybe a little bit longer. So it's not something we would put back just to provide estrogen, but we would put it back when the woman is actively trying to conceive so she can make the most of the two or

three-years that the transplant survives. The best place to transplant is under discussion. For a while, it was transplanted into the arm or under the abdominal skin. These places were convenient for trying to get the eggs out after they matured, but no one has tried to create a baby from tissue under fatty tissue. It looks like for some reason that we don't understand yet, the piece has to be put into the pelvis to work. Maybe it has to do with temperature stability or preen, but it looks at this point like it has to be transplanted back into the abdomen to have a chance of working. The bigger concern is might we give the person cancer back by putting a piece of ovary back. When we know from reviewing the risk of malignancy after organ transplant, sometimes people who are donors -- for example, for a liver, kidney, or heart transplant, are found after the fact to have a small cancer they were not aware of. These cancers can be transmitted with the organ that is transplanted, and the cancer often shows up in what we call ab atypical site. One man who was a heart donor was found after the fact that have a small cancer of his prostate, and the heart that was transplanted developed cancer that looked like prostate cancer. It is possible for lung cancer to be transported in a liver transplant. One organ owner had had a melanoma 16 years previously, and when she died in an accident, each recipient developed melanoma. So how cancer can be transported in begans is not -- in organs is not well understood. CNS tumors are considered one of the highest risks for transported malignancies, and so we are very cautious about the idea of using a piece of ovarian tissue or saving one, and then putting it back into the woman at a later date with the concern that we would give her, her cancer back. I want to touch for a minute on the sharing hope program. This is part of the live strong foundation. Many fertility centers participate. The IVF cycles that I have mentioned as a way of preserving embryos and eggs are not expensive. The total cost is usually about 15 thundershower dollars, about 5 thaw dollars is the -- $5000 is the medications. The centers that participate agree to hold the total cost down to something less than $5000. This makes it manageable for people who haven't had time to save up for an IVF cycle. In order to qualify for the program, there are income restrictions, which I believe are something lick you have to make less than $150,000 a year, you have to have had no previous cancer treatment, your insurance has to refuse to cover it, and you have to be having a treatment that is at risk for causing infertility. The program has been very generous with providing medications and making it possible for patients to start the cycles right away and not interfere with their cancer treatment. For patients who have already completed treatment and not done embryo or egg preservation, when it's time to have a baby, a thorough evaluation for infertility is appropriate. Thyroid dysfunction is very common after radiation treatment to the brain, and a low thyroid function is a common cause for infertility, and is very treatable. Likewise, the prolactin is often inappropriately elevated after radiation treatment to the brain. Prolactin is the hormone that makings you make milk. It should not be present unless pregnant or breast-feeding. There are medicines this can lower this, and sometimes that can result in normal ovulation. A woman or a man who has had radiation or chemotherapy should have evaluation. We evaluate hormone status, whether fallopian tubes are open, and what the man's sperm count is. Women who fail to ovulate may be manageable with injectable fertility drugs. The FSH and LH hormones that are disrupted by radiation treatment are available. They are injectable medications, but they are available, and can be administered and result in normal ovarian function. If the man still makes sperm, but the sperm count is quite low, this can often be managed by artificial insemination with his sperm into his partner or if the sperm count is quite low, that can be managed by in vitro fertilization. Sometimes we do ICSI, intracry to plasmic sperm injection. In that procedure the female partner has an IVF procedure, and each egg

hassen a single sperm injected into it to maximize the chance of fertilization, even with very low sperm counts. Women who have had key month therapy will be affect expected to have decreesed ovarian reserve. That is another name for decreesed numbers of eggs remaining in the ovaries. This is to be expected. The diagnose owe sis should not be a surprise, and should not be a reason not to proceed with infertility treatment. For men who have no sperm, pregnantty is certainly possible if the female partner is inseminated by sperm from a sperm donor. There are several large sperm banks in the country. I have put the website address for one of them. I am not promoting this one, but it's a very nice, representative sperm bank that you can look at their website and get a good idea of what using a sperm donor is all about. For women who have no eggs left and have been diagnosed with ovarian failure, pregnancy is possible using donated eggs. The eggs can be fertilized with the husband's sperm and placed into the woman's uterus, where she can be expected to carry it normally. This process is expensive, in the range of $25,000 per cycle. It has been extremely high success rate, perhaps 60% or 70% chance of success with any two Embry yeses that are transferred -- my before he owes that are -- embryos that are transferred. It is possible to adopt embryos. This is a relatively new process, but is gaining in popularity. There is an organization called the national embryo donation center, centered, I believe, in Tennessee. That is a national clearinghouse for embryos that have been donated. If you qualify for this procedure, the embryo is thawed and placed into the woman's uterus, and she can be expected to carry it normally. The snowflake, organization, I believe, is based in California and is likewise a clearinghouse for embryos that have been donated. The total cost will be in the range of $20,000 for embryo adoption. And if none of those is feasible or desirable, more typical adoption is certainly a way to build a family. I will warn you that normal social services or Catholic charities services can be a problem in a couple where one member has a history of cancer. There is a long waiting list for babies, and the waiting lists tend to be whittled down by declining people who are older, people who have medical conditions, who have a history of serious medical conditions, so it may not be possible to adopt through a social services type agency. However, private adoption does not have these limitations, and it is often possible to adopt that way. In conclusion, treatment of brain tumors has the potential to impact reproductions. Radiation to the brain can have multiple effects, but these can generally be overcouple with current medications. Key month therapy can -- chemotherapy -- should be able to help you navigate through your treatment options. Thank you, and I'd be happy to take questions.

>> Thank you. We Baton Rouge en -- we were enthralled here. We have some questions that have been posted beforehand and has we have been talking. So I will get those to you. Someone is asking if they are at risk, more than average to have a child with complications after having a brain tumor and being on timadar?

>> The question is a little bit hard to answer, and primarily because, of course, 20 years ago, people didn't survive cancer for the most part, and so they didn't have babies afterwards. So what we have is relatively short' term information, but our best information now is keep -- chemotherapy did you not make the pregnancy itself high risk as long as the therapy is long past and you have proper here monial treatment to support the -- here monial treatment -- hormonal treatment.

>> What about -- > The brain MRI is perfectly safe, even if it would be necessary during pregnancy to follow up on some symptoms that have developed and caused a concern about resoutherns or

something. MRI does not involve radiation, so it's felt to be safe in pregnancy. Now, sometimes when they do an MRI, they like to use a contrast agent. We prefer that they nod use that in pregnancy, but it's always a situation where the benefits are weighed against the risks. And the MRI itself is safe. Maybe the contrast should not be used. Now, the gamma knife, what that basically is, is very high dose, focused, radiation. The good news about the gamma knife is it probably is more likely to spare the hypothalamic and pituitary areas and they are not involved, because it is not as prosyce. Gam that knife treatment of the area of the hypothalamus would actually be higher risk of damage to those areas because of how high the dose is.

>> Great. Someone is asking you to explain the connection between hypothyroidism and brain tumors and fertility. In this case, they are asking about a benign brain tumor, but if you have information about those, that would be great.

>> The hypothyroidism is a result of radiation to the hypothalamus or the pituitary area. I'm not sure that would happen with a benign tumor. There are prolactin excreting tumors that damage the pituitary. Those would be tumors that can damage thepy to a Tory and -- pituitary and can result in problems. This is kind of a general thermostat for the body. It regulates everything, including the reproductive system. So women with low high troid function usually dod no ovulate. If they do, they are at higher risk of miscarriage. But hypothyroidism is easy to treat with a small pill taken once a day that is easy to tolerate. So if it's detected, it should be very treatable.

>> Thank you. Someone is mentioning they went through chemo, radiation, and self-transplant at the age of 3, can she increase the chances of being fertile in the future?

>> The important thing would be to know if she has gone through puberty normally. Because in order -- I maybe didn't make this point clearly -- I did try to make the point with men, that they can have perfectly normal hormonal function and have normal sexual function even though they make no sperm. That's not true for women. If women don't have any eggs left, they don't make any estrogen. If they don't make estrogen, they won't have normal puberty. I that won't have a growth spurt, they won't start their periods. If they have those things, breast development, if they start their periods, then they have eggs and they are ovulating. What we know is that women who were treated in childhood are at risk of premature menopause. They should have chair children as early as possible. It would be appropriate for them to check in with a gynecologist early and have their ovarian reserve assessed, knowing in advanced they are likely to be told they have decreesed ovarian reserve. That would give them an idea of how long their ovaries are going to continue to function and what their chances of having a baby in one, five, or ten-years, dependenting on how old they are.

>> There is another one piggy-backing off of them. A a rare tumor, and does not know if the treatment sterilized them. What would you recommend for someone in this situation, starting to think about a family in a few years, finding that they are infertile or not, and what deficits they could be expecting?

>> Again, a woman who goes back to having normal periods, or goes through puberty and develops normal treatment after treatment, is ovulating and is potentially fertile. If she doesn't want to be pregnant, she should use birth control. So the best kind of overall indicator is are you having normal

periods? That usually means you are ovulating and potentially fertile. Now, the use of a new medication -- this is our bugaboo with all of this, the new medication versus with the old one, and the old in combination with the new one, and our general approach is to say all medications are likely to damage some eggs. How many relates to how old you are, exactly what the agent is, it's impossible to know with any given medication, but the best general indicator are -- is, are you having periods.

>> I think that helped clarify for the people who are asking that. Right now, we don't show any questions. If anyone has another question, and wants to type in, we can wait a few moments and see if anything pops up. A transcript of this webinar will be at our website as well as the webinar. So if someone is interested in reading the transcript or having that available, we make sure that we have that for people who have a hearing deficit or people that just want to read your presentation. So we did get a couple more that came in. We do have some time. How long after treatment is it acceptable to start having a family?

>> That is something that we kind of negotiate with the oncologist in every situation. A general rule of thumb is at least two-year -- two years. There is no hard and fast answer to that. My main concern is that you go enough time to know if you have an aggressive tumor that's going to come right back, the last thing you want is to be five months pregnant and find out you have a recurrence, and you have to make a hard decision between saving your own life and saving the baby. So if you let it go a couple of years and everything seems to be stable and fine, that's a situation where it's usually safe to start thinking about having a baby.

>> Okay. And what birth defects should these patients be aware of as possibilities?

>> Well, again, our best information is that key -- keep they were, -- chemo does not increase the risk of birth defects. That's surprising, but very reassuring. All the information out there says if you wait a reasonable length of time, perhaps two-years or more, the risk of birth defects, stillborns, miscarriages, all of those things, is no higher than the average population.

>> Is there any chance, if you could repeat one answer, someone is asking to hear it again, if you don't mind. The question about hypothyroidism, mengiomas and infertility.

>> Hypothyroidism, with or without brain tumors, is a risk factor for infertility. It has a number of effects. The thyroid is kind of a general thermostat for the whole body. It controls many things, including ovulation and reproductions. So people who have low thyroid function, who are hypothyroid, usually dod no ovulate, or if they do ovulate and conceive, there is a higher risk of miscarriage. That is the case whether or not you have been treated for a brain tumor. Now, treatment of a brain tumor with radiation disrupts the regulatory centers in the brain, and one of the most sensitive to be deerupted is the thyroid. So it's a common problem after treatment of brain cancer. If it's a meningioma in a location that is disrupting the pituitary, there may not have been any radiation, but it is disrupting the centers. If hypothyroidism is diagnosed, whether because of a tumor mass effect or whether because of surgical changes are radiation changes, it is very easy to correct with thyroid medication. It comes as a small pill taken once a day. It is very well tolerated, so should be manageable no matter what the cause of it is.

>> All right. That looks like all the questions, we have. Gene, I appreciate your time in doing this for our patients and families. Let's pause for a moment and we will conclude our web their recording -- webinar recording. We invite you to check back at our website for other related topics. If you have missed any of our previous webinars, you can listen to them at our website. More webinars will be presented in 2014, including the cost and risk factors associated with brain tumors and surviverships in brain tumor survivers. This concludes our webinar. Please complete the feedback survey tomorrow. We want to hear what you have to say. You may not disconnect. [Event concluded]