

Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about fertility preservation and cancer with Dr. Cindy Duke and Dr. Ryan Martin. Dr. Duke is clinical instructor in the Department of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine and Dr. Martin is Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences and Medical Director of the Yale Fertility Center of Westport. Here is Dr. Anees Chagpar.

Chagpar Let's start off Cindy, maybe with having you tell us a little bit about why this matters particularly for cancer patients?

Duke One of the reasons that we are happy to be here today is we would like to emphasize that fertility can decline with age and patients who are diagnosed with cancer and are about to undergo therapy, be it chemotherapy, radiation therapy or surgery for their cancers if it is gynecologic cancer, their treatments can further lead to decline or complete loss of fertility if steps are not taken ahead of the treatment.

Chagpar Ryan, can you talk about that little? Supposing I am a woman who was just diagnosed with breast cancer, my head is in the space of, I have breast cancer, I am 23 years old, what am I going to do, and what you are telling me is you need to think ahead of that to say, yes you have got breast cancer and you need to think about whether you ever want to have children in the future?

Martin Yeah, and it is hard to understand once you have reached a big diagnosis like that, you have heard something catastrophic, your mind is wandering around, and one of the things that we are hoping that the oncologist or the care providers are discussing is, this treatment could hurt your future fertility and if you are planning on having kids, this is something that we need to at least talk about now. What we are trying to get the word out about is to say, once you have beaten cancer and the treatments are so good now that it is expected that you are going to do well in many cases, how are you going to live your life afterwards, and if your plan was to have kids, we need to think about that prior to treatment that is going to severely affect the ovaries.

Chagpar Cindy, can you pick up on that point because I think that for some people they may think, okay I am going to prioritize, I am going to fight my cancer first or worry about kids and having more kids later, but what I hearing Ryan say is that is fine, but you need be doing that thinking before you treat

the cancer, is that right?

Duke That is correct, and I know it is hard for most people to appreciate that because certainly your primary focus at that point is surviving cancer and we are on board with that. What we are saying

3:40 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

is when you are faced with the diagnosis of cancer important question is congruent to worrying about the treatment of your cancer is that simple question of what might be the potential thoughts of future family building and you know this includes adolescent and pediatric patients, male and female by the way, it is the question of what about future childbearing, so while a patient who is faced with the diagnosis may not in that moment be thinking about ever having children or if they have started a family continuing to build a family, it is a worthwhile consideration because the treatments can affect your gametes, meaning your eggs if you are female or your sperm if you are a male.

Chagpar So this is a consideration for both genders then, not just women who we usually think about fertility in the realm of breast cancer, cervical cancer, but this is something that we should be thinking about whether you are male or a female and even for kids who are diagnosed with childhood leukemias?

Martin I would say that at the Yale Fertility Center we are dealing with male and female emergencies coming in. For the males, it is a lot less complicated in terms of getting gametes to freeze. For females, it is a little bit more complicated in the fact that we have to stimulate ovaries to generate these eggs. These eggs are basically in a dormant state and need to be stimulated prior to being retrieved and that can take 10-12 days in a typical stimulation cycle, so for men, they can provide us with the sperm sample that we can freeze and that pretty much takes care of their future fertility in terms of preservation. For females, it is a little bit more difficult and that is where we come in.

Chagpar I am going to pick up on the whole timing issues, but let me get back to the childhood cancer issue because for me that was really something that I had not thought about. What do you do for kids who are getting cancers? Thankfully this is rare, but there are still children who get cancers prepubertal, what do you do then?

Duke That is an interesting question and one that faces most fertility specialists. At the moment, if you have not yet entered puberty, so in the case of a young woman we are talking about having started your periods, if you are diagnosed with cancer before you start your period, certainly what Dr. Martin has described which is harvesting eggs or retrieval is more difficult, and actually not possible, so what we offer them is freezing of ovarian tissue. You can freeze a portion of the ovary. Fortunately, the good news is if you are pre-pubertal, usually the effects of chemotherapy are not as toxic or dangerous as they are when they are post-pubertal but the effects are still there and therefore we offer

ovarian tissue freezing. Though it is still in the experimental realm of treatment, it is what we offer at the moment across the country and here at the Yale Fertility Center.

Chagpar So parents should be thinking about that for young girls who have cancers and what do they think about young boys who have not hit puberty yet?

Martin It is a more clear answer for females rather than males in this scenario, but the conversation being had with the patient and with the parents in this scenario is very difficult, very emotional and sort

7:31 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

of a major blind side, thinking about this option in a prepubescent kid is very difficult, so what we typically say is that these are your potential options, one is to freeze ovarian strips and that is something that requires a laparoscopy, so it is not without some difficulty and risk. The other part is you could undergo the toxic chemotherapy and hope that there are not significant effects on the ovaries like Dr. Duke was saying, not always do we have significant effect on the ovaries when we get chemo as a child, but those are 2 main options and I think the hardest part of the whole conversation is talking to the parents and saying, I know that you just received this unbelievable diagnosis and now you have to start thinking about grandchildren and it is a very difficult conversation and one that most parents are not ready to hear about but need to hear about because the options need to happen prior to the treatment so it needs to be talked about.

Chagpar I think the other issue is it is not just talking about grandchildren, it is talking about taking your child who has just been diagnosed with cancer and either subjecting them to a surgery for this ovarian strip harvesting or taking your chances on never having grandchildren, so what are the risks? When you say that chemotherapy may not be as toxic to the ovaries if you have chemotherapy in a prepubertal setting, what numbers do you quote patients and their families because I would think they would want some numbers?

Duke They want numbers, it is hard to actually quote numbers because there are so many variables, so it is not just the type of cancer they are diagnosed with mainly, where is it located, but what treatments are they about to receive, is it just chemotherapy, is it chemotherapy plus radiation, is it radiation that involves direct radiation to the pelvis, i.e., it is in the area where the ovaries are located? And sometimes surgery is needed in preparation for radiation to sort of move the ovaries outside of the field of the radiation, so it is a number of things. It also depends on the age, maybe they are pre-pubertal but close, so peri-puberty, so that would suggest that they are more in that cusp, so that may actually lead to a higher decline. What I would say at this point is, studies have looked at the effect of this discussion on survivors of childhood cancers where survivors of childhood cancers are later asked if you had the opportunity

at the time to talk about your future fertility, would you have liked to know about it? And these were people who, I should, say survived treatment for childhood cancers in the age before we had these options available and they have unequivocally answered that they would prefer to have known and would have liked to have an opportunity to preserve their fertility or at least know about options if they were available.

Martin The other important point that Dr. Duke was alluding to is the type of chemotherapy as well, so there are some chemotherapies that are more gonadotoxic than others, so it would also depend on the treatment regimen and what the plans are.

Chagpar That is an interesting and difficult conversation I can imagine and I suppose the other difficult conversation comes back to one of the things that you commented on earlier, which was the length of time, even in postpubertal women, in order to stimulate their ovaries, to harvest these eggs in

11:32 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

order to freeze them, in order to preserve downstream fertility, that takes time. How much time does that take and how does that gap in time affect their therapies? Is that something that you hear from patients and what do you tell them?

Duke It is a question that we hear from patients and from providers, oncology providers, and it is a valid question. It is one that we work closely with oncology doctors on because certainly the timeline matters and for some patients, for example those diagnosed with certain leukemias, time is of the essence in terms of initiating that chemotherapy treatment and so what we are not saying is that every patient diagnosed with cancer will have enough time to actually undergo the process of retrieving eggs in the case of female patients, but it is one worth talking about. Sometimes, there is not enough time even in patients like the leukemia patients who require chemotherapy induction within a matter of days, but at other times we do forgo the therapy but offer the counseling which both the American Cancer Society and the Society of Reproductive Medicine now recommend to at least counsel patients on the future potential effect of the therapy.

Chagpar What does that counseling entail? If the counselor says, sorry there is no time to preserve your fertility, that is not entirely satisfactory I would think.

Martin It is not always satisfactory, but what I do want to stress is that from the time we get a call from Smilow or any other local oncologist or multiple states surrounding Connecticut, is we see the patient within 24 hours at the Yale Fertility Center, so they call, and we get them in right away. The reason that we do that is that time is of the essence, so we see them right away and if they want to begin treatment, or there is something that they want to start with, we can actually begin the following day. There are companies that we

work with that would donate free gonadotropin medications which can be quite expensive to be sent overnight to the patients to start the stimulation cycle, so typically we can get a cycle done within 12 days, something like that, sometimes less, and if we cannot get a cycle in time based on the oncologic needs, then another option is to freeze eggs.

Chagpar We are going to talk more about all of the options and how it affects our cancer patients right after we take a short break for medical minute. Please stay tuned to learn more information with my guests, Dr. Martin and Dr. Duke on fertility preservation.

Medical Minute The American Cancer Society estimates that there will be 75,000 new cases of melanoma in the US this year with over a 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for melanoma. The goal of the Specialized Programs of Research Excellence, SPORE, in skin cancer grant is to better understand the biology of skin cancer with a focus on discovering targets

15:13 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

that will lead to improved diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guests, Dr. Cindy Duke and Dr. Ryan Martin. We are talking about fertility preservation in cancer patients and right before the break we talked a little bit about when time is of the essence, so you have just been diagnosed with cancer but you are young and you are thinking, I might want to have a family in due course and the importance of getting into a fertility specialist to talk about options beforehand and Ryan, one of the things that we said just to clarify was that if you do not have time for ovarian stimulation you could have ovarian tissue preserved, is that right?

Martin Yes, in situations where the oncologic treatment needs to happen in such a rapid pace that we do not have time to stimulate the ovaries, the other potential option in that scenario is to take ovarian tissue out and freeze that for later use. We would recommend that in situations where we just could not get to the stimulation because of the necessity of rapid oncologic treatment.

Chagpar Cindy, can you talk a little bit about advantages and disadvantages of each technique? Certainly when timing is of the essence, you might want to

take ovarian strips, but are there advantages of one technique over the other in terms of fertility, in terms of how it works?

Duke Absolutely, and the gold standard for treatment like we mentioned is embryo freezing if possible or egg freezing and what that specifically addresses is the future childbearing, so the ability to become a parent, a biologic parent later on, if we freeze eggs or embryos. The added benefit to having that option with freezing ovarian tissue is if a woman becomes menopausal after she completed her chemotherapy, having frozen ovarian tissue allows the ability to replace ovarian tissue that is still hormonally functional and thereby we are able to help reverse her menopause if that is a desire, we are able to also resume her menstrual cycle which would have stopped if she became menopausal as well to allow her to ovulate or allow her to undergo IVF later on. So there are added benefits to freezing ovarian tissues; however, there are also potential draw backs to freezing ovarian tissue. For example, in patients who may have cancer that actually affects the ovaries, cancer of the ovary or leukemia or lymphoma that could have potentially gone to the ovary or breast cancer that could have gone to the ovary, the risk we run is when we replace that ovarian tissue after she has been cured of her cancer as we could reintroduce the cancer into her body and so that is why sometimes even if the tissue is frozen, it may never be replaced for that risk, so while it is an option that is being utilized around the world at the moment, it is nowhere near as frequently as egg freezing or embryo freezing, we also do have to be cautious in when and who, which patients we replace it into.

18:57 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

Chagpar Before the break we were talking a lot about egg preservation and harvesting eggs, but now you are bringing up this concept of embryos, that I think for some people may have ethical overtones and implications, can you talk a little bit about that process and what that conversations with patients and their families is like?

Martin Patients basically have 2 main options, one is to freeze their eggs or to freeze fertilized eggs, i.e., embryos. Frozen eggs and freezing and thawing them used to be experimental up to a few years ago, right now it is a standard of care, and we do it quite often at Yale now. Freezing embryos is the gold standard that has been done for years and is highly successful. If you think about that, you are an egg, not every single egg has the capability of becoming a live birth, whereas an embryo is already a fertilized egg and has made it through several steps and is already beginning to function, so you have much higher chance of getting pregnant with one embryo than with one egg, so what we would typically talk to patients about is if you are married or if you have a significant partner, freezing embryos is the preferred method if you are thinking about future childbearing. If you are a single patient or young and single, then the options are to freeze your eggs or we have many patients that will actually use donor sperm to create embryos because they know it is far more successful

than freezing eggs alone, so those are the 2 main options and yes it does bring in some more questions and some questions about how do they feel about their future childbearing, how do they feel about making an embryo with someone they have never met, all these things are very difficult things to think about but in terms of us counseling patients they need to know all their options because some patients would find one thing far more appropriate for them than others.

Chagpar In terms of how this works, creating embryos to freeze, you would stimulate the ovaries and then what?

Duke For both patients we will stimulate the ovaries, meaning the patient whom we are planning to either freeze eggs or go on to make embryos prior to freezing, we will stimulate the ovaries with injectable medications that typically last somewhere between 9 to 12 days of stimulation. During the time of stimulation you undergo a series of ultrasounds to see how the ovaries are responding to the medications and once the ovaries are ready, meaning the ultrasound shows us measurements that we know correspond to eggs being ready for harvest, we bring the patients in, it is an ambulatory procedure, meaning they just come to the office, under light anesthesia, they undergo an ultrasound guided suction, meaning we use an ultrasound in the vagina and a small needle, we suck out the eggs, and at that point if the patient is about to undergo chemotherapy, that sort of ends her needing to continue at the clinic. She can move on to start her therapy while the rest of the process continues. The rest of the process, if she were just freezing eggs, is identifying the eggs, identifying what type of eggs they are, are they mature enough or a little bit immature, those are then aliquoted, or put into tubes and frozen and they can be used in perpetuity. There is no time limit on how long they can be frozen for. If the patient has a partner or has identified a sperm source, i.e., a donor, the eggs that she has go on to be fertilized in the embryology lab and they are

23:11 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20 Drs%20Duke%20and%20Martin_235254_5.mp3

then frozen somewhere between 2-3 days later and again they can be frozen for as long as it is needed at this point, but in terms of patient involvement, once the eggs are harvested, she can move on to her therapy. I would also like to piggyback on what Ryan was saying and point out that for some patients they also chose to do a split, meaning they freeze some eggs and some embryos.

Chagpar In terms of the process, two questions, the first question is the ovarian stimulation, the injectable medications that you talk about to stimulate these ovaries, these are hormones right, which for many patients who are suffering from things like breast cancer may actually be the cause or may have increased their risk of developing breast cancer, do you get patients giving you a little bit of push back about jeez, what is this going to do to my breast cancer?

Martin In the lay press, the word hormone has become a bad word and I think that is mostly lack of understanding as to what these studies that were talked about really mean, but what we are talking about is we can completely replicate

follicle stimulating hormone which is the same hormone that your brain tells your ovaries to make eggs, we can just replicate it and use it as an injectable source and once you inject it, it tells the ovaries to grow more than one egg which is what we are looking for. In situations where medically it is not a good idea to increase the estrogen or the progesterone, towards the end of the cycle what we use is another oral medication to keep the estrogen levels low to allay fears and/or if the oncologic team has suggested to do it, we do that and there is no data out there right now telling us that 10 days of injectable medications leading to transiently elevated estradiol would do anything to the oncologic process, but in situations where the patient does not want to potentially incur a risk or the oncologic team does not want you do it, we just add this oral medication to the treatment which does not affect its efficacy.

Chagpar Excellent, and one other question is you mentioned that the eggs can be frozen in perpetuity.

Duke Correct.

Chagpar Embryos too?

Duke Yes.

Chagpar Then the question becomes, where do these embryos sit and what happens if you do not use them and what are the moral and ethical implications of that because I can just see that people may be wondering about all of that?

Martin Whenever a cycle is going on whether it is for fertility or for oncologic reasons and fertility preservation, part of the detailed discussion that we have is about these issues and we also have plenty of documentation to say these are your potential options in the future, what would you like to do? And so there are potential options such as discarding embryos or donating to research.

26:40 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201018%20YCC%20Answers%20-%20Drs%20Duke%20and%20Martin_235254_5.mp3

Duke Including what happens to the embryos if the couple were to split.

Martin Exactly, we have to discuss that, so in the case where the couple splits, these are our wishes, so we have all these forms that are filled out for these very reasons, I mean once you create embryos they are no longer one person.

Duke It belongs to two people unless it is a donor.

Martin Unless it is a donor, but technically it is a team, so the idea is that you have to discuss these issues ahead of time, so patients that are not intending to use the embryos that they have or not intending to use all of these embryos, they can donate to couples anonymously, they can donate to research, they can discard them, so patients that have difficulty with the idea that they would have remaining embryos left over, sometimes elect to not attempt to fertilize that many eggs for fear of having to make this decision that may be a big deal

for them, that does not typically happen in the oncologic fertility preservation world, but it certainly does happen on occasion in the fertility IVF world.

Chagpar I can just imagine that these are such difficult and heavy discussions to have right in the midst of a cancer diagnosis, my head would just be spinning on top of which there likely are financial implications, I mean the freezers have got to cost something right, so what is the cost of all of this on top of people thinking about the cost of their chemotherapy and the cost of their radiation, but now there is cost of not only the fertility preservation procedure, harvesting eggs or embryos and then the cost of storing, can you speak to that?

Duke The costs vary, before I talk about cost I wish to also point out that yes we totally understand just how tough this process is emotionally for the patient and partner and extended family and as a result, our team is actually comprised of a number of members, so not just physicians but nurses who are very well versed in working with this specific patient population, we have a social worker who is part of the team whose job is to help assess psychologically this potential loss of fertility and the meaning of that to patients whether they were thinking about it or not and in terms of cost, it is variable, but we have a number of things that can be addressed including programs to help with getting medications for free, freezing eggs, the process of just the freezers is about as much as \$600 per year to freeze the eggs but again, it varies.

Dr. Cindy Duke is Clinical Instructor in the Department of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine and Dr. Ryan Martin is Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences and Medical Director of the Yale Fertility Center of Westport. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber, hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.