

Yale CANCER CENTER *answers*

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Hosts

Anees Chagpar MD

Associate Professor of
Surgical Oncology

Francine Foss MD

Professor of Hematology

Steven Gore MD

Director of
Hematological
Malignancies

Fertility Preservation

Guest Experts:

Cindy Duke, MD, PhD,

*Clinical Instructor in the Department of
Obstetrics, Gynecology and Reproductive
Sciences at Yale School of Medicine*

Lubna Pal, MD

*Associate Professor of Obstetrics, Gynecology and
Reproductive Sciences*

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. 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 can 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 options for cancer patients with Dr. Lubna Pal and Dr. Cindy Duke. Dr. Pal is Associate Professor of Obstetrics, Gynecology and Reproductive Sciences and Dr. Duke is Clinical Instructor in the Department of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine. Here is Dr. Steven Gore.

- Gore This is such an important area and I am so glad you are here because, of course, in my practice, which is hematologic malignancies, we have a lot of younger patients who are being treated for leukemia or lymphoma. This is something that all patients are worrying about and so what do we do, who is a candidate for fertility preservation and who should be thinking about it?
- Duke Quite honestly most patients of reproductive age, and by reproductive age we define that as patients anywhere from birth through age 40-45. Certainly for a patient with cancer it is a big consideration, particularly if they had not given thought to family building prior to the diagnosis. I think any patient in that age range is at least a candidate for counseling.
- Gore Let's start with adult patients, because I had not even thought about the pediatric issues, and it just shows how I think about my own world. I am typically faced with an adult patient of reproductive age who is facing a hematologic emergency, that is they have got a cancer that needs to be treated and what should I tell the patient, if they are going to get chemotherapy, are they necessarily going to become infertile?
- Duke Honestly that depends on the therapy being offered, so all chemotherapeutic drugs are not equal and neither is radiation therapy. So in terms of the patient, there are a number of factors that go into the counseling, that includes age of the patient, the drug, the agent being used, certain classes of chemotherapeutic drugs such as the alkylating agents which include things like cyclophosphamide and ifosfamide are known to be greater risks to ovarian functions, specifically in terms of risk related to developing menopause and infertility in the future. Other risks include the amount of the drugs, so not just the type of drug but the dose of the drug or the duration of therapy and in the case of radiation, likewise, the dose of the radiation.
- Pal Yeah, and something worth mentioning, is that while our focus is women, I do believe men cannot be ignored, young men and young women.
- Gore I was going to say something about that.

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- Pal So there are two concepts, one is that the disease itself may have detrimental implications for gamete biopsy. So cancer diagnosis in and of itself, there is plenty of data to support by the time somebody is sick enough to be diagnosed, already the sperm are being compromised and already the ovarian function has been compromised. Now the difference here is men are making sperm all the time, but women are born with a retirement account, if you will. So the damage to female biology has much more lasting implications than to men's biology and that needs to be appreciated.
- Gore Hmm.
- Pal Secondly, the severity of disease at the time of presentation. And thirdly, as Cindy mentioned, all aspects need to be entertained, we are focusing so much on improving longevity and we are succeeding, but it is the quality of that life, now that we have gained longevity, what is happening to that individual and reproductive function, parenting and ovarian biology, which translates into overall health, so early menopause relates to a slew of medical problems. So even though we are talking fertility preservation, we are really talking about quality of life and health of the individual.
- Gore Interesting, getting back to men for just a second. I was taught a long time ago, and maybe it is not true anymore, that because what you mentioned that the quality of the sperm production is often compromised in somebody who is acutely ill with something like acute leukemia, at my former institution, Johns Hopkins, in general we did not recommend semen banking at the time of diagnosis, has that changed at all?
- Pal A few technological advances that have really happened over the last 20 years or so, not that I am dating us here, but you need five sperm to be able to fertilize five eggs to achieve a live birth. We are in such a different place now, and you are absolutely right, compromised semen when frozen may yield very poor numbers, but you would still get a few live sperm.
- Gore That is all it takes.
- Pal That could be all it takes, whereas the prognosis, depending if you were going to do whole body radiation, which is it for that guy.
- Gore Right, so it really pays.
- Pal It pays to save. There are plenty of patients who have survived and are in a better place, have recovered, spermatogenesis has recovered, not to a normal range but to a range that we can achieve pregnancy, and we always recommend going with the fresh sperm, but in the event that it does not recover, it pays to have something.
- Gore Money in the bank, so to speak.

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Pal Absolutely.

Gore That is probably a joke you guys say all the time.

Pal It is, but people understand it so much more, it is so palpable.

Gore What do we do, can I get a consultation for patients at any time in this kind of situation?

Duke We offer a 24-hour, 7-day per week service here at Yale Cancer Center. We see patients both as outpatient, and inpatient, so oftentimes, a newer patient population included, the diagnosis is made while the patient is admitted to the hospital and their therapy is initiated during that first admission, so we would actually come to the patient, and in terms of our male patients, we have a sister service that is part of the umbrella of our fertility center. A brother service, actually, and they offer the sperm banking or cryopreservation services, but as the fellows on their service, we still serve as part of that initial consult.

Gore Interesting, I guess for our listeners and hopefully none of them have cancer, but unfortunately, we know that some people will and I can say as a practitioner that it always helps me when a patient brings up the fertility issue just because that is something that people think about a lot by themselves and we are so busy trying to save the patient's life all the time that is not always the first thing, and we are trying to get better about that.

Pal I think from our end that really is the message that we need to be disseminated. It is the patient's prerogative. People need to be aware what technology can offer them and we as providers need to put on the table long-term implications for reproduction, recognizing that patients are dealing with life and death at that moment, but part of our responsibility is at least putting it on the table for patients to consider. There is plenty of literature to support survivors. The one thing that they verbalize frustration with is, I wish somebody had included me in the decision making.

Gore: At least brought it up, right?

Pal Absolutely, and the options really from the time delay perspective for men, a single day a few hours is all that needs for them to bank something. For women, at an average, it takes about a week to 10 days, but you can expedite options to match the needs of urgency for the patient provided that is what the patient is seeking.

Gore What are we talking about for women? What are the options for a younger adult woman who wants to maximize her fertility preservation, but needs semi-urgent treatment, say?

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Duke Recognizing that need, we have a number of streamlined processes. The gold standard for fertility preservation in a young women is embryo cryopreservation which means harvesting eggs from a patient and that takes anywhere between 7-10 days as Dr. Pal alluded to and then pairing it with sperm and producing embryos that we then freeze so the patient can access them following her treatment; however, in a patient who does not have a partner or for younger patients, we offer oocyte or egg freezing which is much less with embryo freezing, we can harvest the eggs and then freeze those. Once the patient is better and ready to start her family, then we thaw the eggs, fertilize them with either her partner's sperm or if she still does not have a partner, we offer donor sperm that she can chose from and make an embryo and then transfer that embryo into her uterus and she gets pregnant and carries a baby. Those are the primary options. Other options include ovarian tissue freezing, so for the patient who may be undergoing surgery to remove her ovaries, we can freeze some strips of tissue from her ovary and later on reimplant that.

Gore Interesting.

Duke Other options would include use of medications. This is the most utilized method here at Yale Cancer Center, use of medications to suppress ovarian function prior to initiation of therapy; however, although the data says it is good and it has been looked at for effectiveness for resumption of menses or return of period, there is not enough data yet to speak to whether or not this is sufficient to improve return of fertility for the patient.

Gore Let's go back to this egg harvesting we talked about. How do you do that? You said 7 to 10 days, do the women have to take hormones like you would if you were getting ready for in vitro?

Duke Correct, it is similar to in vitro, so the principles are the same in that we give the women medications to help stimulate her ovaries, to stimulate a pool of eggs, so that we can then mature them somewhat and retrieve them. In terms of egg harvesting for egg freezing, we retrieve them slightly earlier than we would if we were going on to IVF for embryo development.

Gore Oh.

Duke And then we freeze those. The data is actually really good in terms of the ability to thaw those eggs and then fertilize them later, so it is actually considered standard of care now.

Pal That sums it up, thanks Cindy. If I could, just to clarify for the people who are on the other end, in female biology, every month there is a little marathon happening in our ovaries. A bunch of eggs start to grow, but one continues to grow and that growth sprint is about a two week period in female biology. So it is like a marathon, only one is the winner, everything else just stops down at multiple stages and fertility treatment aims at harvesting and sort of salvaging the entire group of runners to continue the run. In a healthy female who is undergoing a fertility related procedure because she is keen on getting pregnant, we have all the time on our hands so we capture those runners, let them run until the maximal time point where we have a good group of larger sized

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ovarian follicles developing and then it is a simple office procedure where transvaginally, under ultrasound guidance, patients are awake, they are a little bit sedated, and we do a procedure where we go and collect the eggs transvaginally with an ultrasound-guided needle through the wall of the vagina into the ovaries to suck out the eggs. So the scientific aspect is the same, but depending on the urgency of time that we have for a sicker patient, we can really expedite the race a little bit. We do not have to capture all the runners. We can go and capture whatever is available to us.

Gore Hmm.

Pal If we end up getting immature eggs, we can even mature them in vitro, outside the body to allow them to reach a point where freezing would be optimal. So we have strategies for using certain medications for women such as with a breast cancer diagnosis where we do not want too high of a hormone level within the patient's body so we can use agents that actually continue the running but dampen her own hormonal profile, so we can strategize and utilize the protocol. Again, the goal is if a patient perceives that that is her choice and if her oncologist perceives that there is that time flexibility available, it can be expedited in a very safe manner.

Gore This is fascinating and we want to talk more about this after the break for sure, but right now we need to take a short break for a medical minute. Please stay tuned to learn more information about fertility preservation options for cancer patients with Drs. Duke and Pal.

*Medical
Minute*

There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment for cancer is an exciting milestone but cancer and its treatment can be a life changing experience. Following treatment, cancer survivors can face several long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers to keep cancer survivors well and focused on healthy living. The Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life and longevity. 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 the WNPR, Connecticut's public media source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my guests, Dr. Cindy Duke and Dr. Lubna Pal. We are discussing fertility preservation. Cindy and Lubna, before the break you were presenting me with very fascinating information about how you can harvest these reasonably immature eggs and cryopreserve them or freeze them viably, what is the success rate of using such eggs down the road when the person is ready to conceive?

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- Duke We measure our success rates by looking at the potential for live birth so a take home baby and the success rate is between 25 and 40%, so if we are successfully able to thaw, 25 to 40% of the eggs can be fertilized and implanted and result in a live baby and the success rates for thaw rates are pretty high even around the country and around the world actually.
- Pal Just to expand on that, until a couple of years back, oocyte (egg) cryopreservation was experimental. Now it is considered standard of care because the yield is phenomenally high in terms of technological advances, so there are parts of the world where oocyte banking is now happening, including our center where women at different stages of reproductive life, who are not ready to move on with fertility just yet, either they do not have a partner or they are being committed to a career where they have to postpone things for a while, women have an option of just banking their eggs for a future use in the event that they have problems with fertility.
- Gore When you say it is in the range of 25 to 40% success rate, is that per attempt or is that sort of the big picture, about a 40% chance of getting pregnant at some point.
- Pal So crudely speaking
- Gore Of course.
- Pal Pound for pound, embryo cryopreservation gives you a much higher likelihood for success than egg cryopreservation, so the only reason to freeze the single cell egg is when you do not have a sperm available to fertilize it. And that is really when you are a single woman without a commitment to a sperm source.
- Duke Or an adolescent.
- Pal Even adolescents, right, no sperm is the reason.
- Gore Is it ever practiced that people get donor sperm when they are single at this stage of the game knowing that they might eventually have a partner or is that really not considered the edge of ethics?
- Pal I have to say ethics is a fine line. It is really the patient's prerogative. I personally have had patients, single women, who chose to undergo donor sperm related fertility treatment, have undergone egg retrieval and have banked a few eggs for the possibility if they come across somebody and want to have a child with that partner, but still are ready in their life to pursue fertility, so they choose to move on with donor sperm but yet have something in the bank for that eventuality.

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Duke And likewise for the patient who has a partner, some of them choose to do half as embryo, so fertilize half and freeze the other half as eggs.

Gore Really?

Pal That really does not say much for the relationship but an occasional patient may.

Gore I see, I thought you were just thinking that the priority would be, you know, if they could have a baby the natural way in the future, that would be preferable or something. I see, saving for a rainy day again.

Duke Again, it is patient driven so they decide, there are many permutations and they pick how they want it to happen.

Gore Fascinating. Let's talk about a younger girl, we have got prepubescent girls and then we have post-puberty girls, adolescent girls, who unfortunately have cancer and need to be treated aggressively, what are the issues there?

Pal There are a number of factors to think of, certainly in a prepubescent or post-pubescent adolescent girl we are also talking about broaching the topic of childbearing in someone who has never considered it. So a lot of this decision making is also borne by the parents or the caregiver, so it is a family discussion. It is a discussion recognizing that they may be a surrogate making a decision for a much younger patient who will then revisit the idea later, so again a sort 'rainy day' savings account and planning ahead for potential wishes of this patient. Certainly with a prepubertal patient, some of the challenges to fertility preservation are that this patient has not undergone puberty yet so that pool of eggs has not started, they are all lined up at the race. However, it is important to also remember that she still was born with a finite number of runners and so therapy, although less likely to effect her eggs as if she were post-pubertal, still effects it. So there are things that we do to protect patients, including if they are about to receive radiation, doing gonadal shielding, surgery sometimes for patients where we life the ovaries outside of the field of radiation.

Gore Wow!

Pal Called transposition of the ovaries, so those are some options and also tissue freezing if it came to it, we can certainly take strips of ovarian tissue and freeze them for the patient.

Duke Our options are limited for prepubescent kids, we have ovarian tissue cryopreservation and other than the physical maneuvers of shielding the area from radiation exposure, an important consideration is what kind of cancer because certain types of cancers do metastasize to the ovary, such as lymphomas, for example.

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- Gore Interesting
- Duke So that needs to be considered, I can salvage and save the tissue, but what if the tissue has cancer in it? One also has to keep in mind what kind of cancer you are dealing with, and this is the experimental realm now. It is an option available and we at Yale are offering, ovarian tissue cryopreservation, but as an experimental strategy because we have not had live births. The patients have not come back and had their tissue re-transplanted for us to get an idea of success but multiple reports have happened. But for prepubescent kids, a consideration about the type of cancer that could potentially involve the ovarian tissue is a consideration. Anecdotally, and again experimentally, harvesting immature eggs from that ovarian tissue so that you are completely removing that likelihood of contamination by cancer cells, has been described. We are not doing that yet at Yale but in literature that has been described as a potential strategy. So families just need to be aware of that.
- Gore But unless they are getting stem cell transplants or a lot of radiation, many young girls will recover fertilities right after treatment?
- Pal As Cindy has said, the younger you are the chances of residual salvage and spontaneous resumption is much higher. Unfortunately, there is no globe for us to look into to say this is a kid who will be completely fine and even though the survivors have resumption or initiation of spontaneous menses, their long term reproductive hiatus tends to be shorter.
- Gore So they have a shorter window.
- Pal The dialogue still should be happening, these are girls maybe in their early to mid-20s who should be planning their reproductive future, as opposed to their peers.
- Gore Their biological clock is ticking faster.
- Pal Right.
- Duke As premature menopause may be a factor for them.
- Gore Do you actually screen for that or just let them know, if you are having hot flashes, take it seriously.
- Pal It is a great question and in some ways it is even a more profound question than addressing fertility preservation because your ovarian hormonal profile has implications for the rest of your biology and by the time we are catching hot flashes and irregular periods we have already missed the boat, so I think counseling every visit, and assessments need to happen every visit, the patients need to be sensitized as to what to be looking out for.

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- Duke That includes things like, have your periods changed? It is great that they came back, but are they regular or are you noticing them spacing out or getting really close together? These things tend to predate even the hot flashes and sleep disturbances.
- Pal And yet another thing, some young girls decide to use contraceptives as a lifestyle choice, and their innate biology gets masked, so you do not know what is happening when you are having withdrawal bleeding on contraceptives. So unless, I the clinician, am sensitized to bringing this up, if a kid comes from a family where the mother became menopausal at age 38 and now the kid has gone through this exposure, chances are that for her lifetime she may have an even shorter window. But at the end of the day the discussion really is about hormones you can address, you can optimize in an artificial way, but gametes you cannot do much.
- Gore For the girl or young woman who chooses to be on oral contraceptives, once they are on the hormonal intervention, you cannot really monitor what is going on, is that right?
- Pal Not reliably, no.
- Duke But one strong recommendation has been to maybe at the start of therapy and following therapy, at least one marker which is anti-Mullerian hormone, or AMH level.
- Gore Mullerian is that?
- Duke Mullerian, yes. It is anti-Mullerian hormone and this is a hormone that is actually made by the ovaries and it is a very good marker for the potential number of eggs, so the pool, the number of marathoners.
- Pal Yet another caveat though, AMH is a reliable marker for egg quantity.
- Duke Correct.
- Pal It is not a reliable marker when somebody is using hormonal contraceptives because again it is those marathon runners, they need to run a little bit to be producing this marker. So when you are on a contraceptive for years at a stretch, hormonal contraceptive, everything gets slowed down.
- Gore Gotcha.
- Pal So it is no more reliable. Secondly, somebody who is really sick at the time of their presentation, girls tend to start having irregular periods or stop having their periods when they present with the cancer type diagnosis. And at that point too, AMH may not be a reliable reflector but that is all that we have right now as one of the most sensitive available biomarkers for egg quantity.

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- Gore Do you recommend alternative contraceptive choices for these young women?
- Pal We recommend a reliable contraceptive, so a hormonal contraceptive is an excellent choice. It is not that it is harming them, it is just mitigating the underlying manifestation. So it is not that you want that flag to be raised because your clinical surveillance, at the end of the day, it was what kind of cancer, when was she presented, how much was the radiation, how much was the dose, what kind of chemo, so that builds up her profile. So I do believe reliable contraception and if that is hormonal, then she takes hormonal, little bit of estrogen based hormonal contraceptive approach also adds to her skeletal well being but it is not comparable to your endogenous, your own hormones.
- Gone How widespread is the knowledge among gynecologists about how to manage women who are cancer survivors? I mean, I have to tell you having been at Yale only for 11 months now, I am really impressed with the approach here which is much more aggressive than the institution from which I came in terms of attention both to fertility preservation and this kind of post survivorship attention to reproductive function. If many of my patients were followed by their gynecologists in the community, I have always sort of assumed they knew what to do, is that the case?
- Duke I think it is variable. I could not tell you an exact number of our community of providers that have a standard procedure, so I would say it is variable; however, that is part of one of the things we are doing which is working to increase awareness and some uniformity in terms of the standard across the community.
- Pal I would concur with Cindy but at the same time say that I think the awareness needs to be better all around, not just amongst OB/GYNs but also amongst oncologists because I think there needs to be a dialogue.

Dr. Lubna Pal is Associate Professor of Obstetrics, Gynecology and Reproductive Science and Dr. Cindy Duke is Clinical Instructor in the Department of Obstetrics, Gynecology and Reproductive Science at Yale School of Medicine. 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. 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 addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.