

BONNIE PATEL: Good afternoon, everyone. Thank you so much for having me. I'm just thrilled to be talking about fertility preservation in breast cancer patients who are undergoing chemotherapy. It's a topic that I'm very passionate about and my partners are very passionate about. So thank you so much. I have no disclosures or conflicts of interest.

So I'm actually going to do things a little bit differently and start out with a question. You can switch. So this is to any cancer-providing physician or nurse out there. I routinely counsel all patients of reproductive age on their fertility options and make referrals when appropriate. OK. Oh, can we go back? OK.

All right, so fertility preservation is a central element of survivorship in the more than 25,000 women of reproductive age who are diagnosed with breast cancer every single year. And actually, 15% of all breast cancers occur in women of reproductive age. And it's actually the most common diagnosis of malignancy in this population.

So it's also compounded by the fact that in today's day and age, more and more women are deferring childbearing until their education has been completed, until their careers have been established, compounded by the fact that survivorship in breast cancer patients have improved. So it's not uncommon nowadays for patients who've completed their cancer therapy to desire to have children. And not being able to do so can be emotionally devastating. So I'm going to propose to everyone-- and we'll go over the data-- that every single provider, every single provider that counsels these patients should be outlining the possible risk of infertility, counseling them on their options, and then making referrals when appropriate.

Patient perceptions are actually, obviously, very important with regards to this. So Ruddy and in 2014 surveyed 620 women under the age of 40 with a new diagnosis of early stage breast cancer. And they found that only 68% of patients that reported back actually reported that they had had any form of counseling with regards to fertility, with regards to their fertility preservation options with their oncologists. There was a greater concern amongst patients of younger age, for obvious reasons, nonwhite race because there are certain cultures that emphasize motherhood more than other cultures, not having had children before, and the receipt of chemotherapy.

Provider attitudes are actually no different from what we just asked to begin with. So Quinn and colleagues in 2009 administered a 58-item survey nationwide to oncologists-- surgical oncologists, medical oncologists, and were basically asking about how often do you adhere to the 2006 ASCO guidelines, which recommend fertility preservation counseling as well as referral when appropriate. And only 47% of respondents routinely referred cancer patients of childbearing age to a reproductive endocrinologist. Referrals were more likely amongst female physicians, those with favorable attitudes, obviously, and those whose patients actually asked about fertility preservation.

One striking statistic of this was that only 18% of respondents actually adhered to the 2006 guidelines. And 37.8% of responders were not even aware that such guidelines existed.

It's actually quite difficult to counsel a patient. A patient walks into your office, has a diagnosis of early stage breast cancer. What is her impact on fertility? How do you counsel this patient? It's difficult to really ascertain because there is a paucity of breast-cancer-specific data. A lot of the data that are available in the literature focuses on hematologic malignancies, which are often present in younger patients.

And then there's a question of the right metrics. So a lot of the studies focus on whether this patient resumes her menses after chemotherapy. And that's not necessarily the right metric to gauge fertility. We see patients all the time that are having completely regular periods, and they're infertile because of decreased ovarian reserve.

Lastly, there is a heterogeneity of patient and outcome. So a lot of this is driven by age and the type of chemotherapy that they're receiving. We know the younger the age of the patient at the time of diagnosis, the more improved her outcomes are. So chemotherapy-related amenorrhea is 10 times more likely in patients who are above the age of 35, between 35 and 39, compared to less than 35. And it's 39 times more likely in patients who are age 40 to 44 years compared to younger patients.

A study out of Norway-- so Norway has a large database registry. And they found, as expected, that pregnancy rates are much lower in patients who are cancer survivors compared to patients who are not. It makes sense. These patients have put their bodies through a lot. They're undergoing chemotherapy. What was interesting though was that the hazard ratio for pregnancy and breast cancer survivors was much lower. It was actually one of the lowest out of all the categories studied.

They then stratified based on decade. And they found that, actually, in more recent years, from 2001 to 2004, the hazard ratio was lower than it's ever been. So why would that be? Well, again, it might be because more and more patients are delaying childbearing so nulliparity is a risk factor for breast cancer. It may be that we are now treating breast cancers very aggressively at earlier stages than they have in the past. That could be a possibility. It was just an interesting finding.

Chemotherapy-related amenorrhea-- so the agents that are most implicated in this are any form of alkylating agents or cyclophosphamides. Cyclophosphamide is used in a lot of breast cancer regimens. And so we can see over here that it's age-related. Above the age of 40, receiving cyclophosphamide is essentially putting an end to your fertility. And you may not even resume menses after that, so 80% to 100% of prolonged chemotherapy-related amenorrhea compared to patients who are younger.

The risk of chemotherapy-related amenorrhea, as I outlined earlier, age dependent, of course, but also the cumulative dose of cyclophosphamide. So patients who are administered CMF have significantly higher rates of chemotherapy-related amenorrhea than patients who are undergoing the doxorubicin/cyclophosphamide protocol.

Addition of a taxane to an AC regimen may actually compound gonadotoxicity. And this has been shown in most studies, but not all of them. The gonadotoxic effects of platinum agents are also unclear. We're using them more and more for patients who are BRCA positive. But again, we don't know how gonadotoxic they are. Some studies show that they may be more gonadotoxic than others.

And then there is no significant additive impact on a amenorrhea with treatment of one year of Herceptin in patients who are HR2 positive. And whatever small increases that some studies have found maybe driven by the Paclitaxel and not necessarily the Herceptin.

How should we counsel patients about resuming menses? When will most patients resume menses? So Su et al. followed 109 premenopausal patients with breast cancer with a median age of 39 1/2 years. And they found that 88% of patients experience at least three months of amenorrhea while undergoing chemotherapy. What they interestingly found was there were no discernible differences in fertility between the patients who lost versus maintained menstruation. It's kind of counterintuitive. You would think if you maintain menstruation, you probably have a higher likelihood of fertility. But that's not the case.

62% of patients usually resume menses within six months. An additional 31% between 6 to 12 months, and only 7% of patients ever resume menses beyond 12 months. So essentially, if you have not resumed menses after 12 months of amenorrhea after completion of chemotherapy, prognosis is very poor.

Predictive factors for resumption include age, pretreatment ovarian reserve, or AMH, anti-Mullerian Hormone levels. So it makes sense. The higher your pretreatment ovarian reserve, the higher likelihood that you will resume menses. BMI, elevated BMI is predictive of resumption, as well as the type of regimen. Again, alkylating agents are damaging.

So I would propose that an approach to fertility preservation should be that all oncologists or any care provider counseling these patients as a part of informed consent, as a part of decision-making, should counsel these patients that these treatments might render them infertile. They should be able to counsel them what their fertility preservation options are. And finally, they should also be able to refer to a reproductive endocrinologist when appropriate.

The gold standard for fertility preservation is fertility prior preservation. So we are able to cryopreserve embryos. We can cryopreserve oocytes. And we can cryopreserve ovarian tissue. So these are the options for women, essentially.

The gold standard, like I said, is cryopreservation. So a patient would undergo hormonal stimulation with gonadotropins for about two to three weeks. Once her follicles are large enough, we would then take her to egg retrieval, retrieve all the oocytes, and then freeze off all the eggs.

There is a newer option where now we can actually take parts of the cortex out from the ovary and retransplant back at later ages, whenever the patient is ready for childbearing. This is very controversial. And it actually has not been done in breast cancer patients just because of the risk of reseeding.

Embryo banking, as I said, gold standard. It's a well-established technique with a very high survival rate of embryos after thawing, over 90% survival. But the downside is the patient needs to either have a partner or to use donor sperm in order to create embryos, which not all patients are willing to do.

Next question. So if a patient of reproductive age does not have a partner, I do not recommend egg freezing to her, as it is experimental.

Well, that's very good. It is no longer considered to be experimental. It is a perfectly validated technique for fertility preservation. It was considered experimental because previously, we've been fraught with a lot of challenges. Eggs are very difficult to freeze because they have a very high water content. You can imagine. If you brought eggs from the grocery store and tried to put them in the freezer what would happen. Right? They would explode because a lot of ice would form. Ice is not good for intracellular organelles. So because of the susceptibility to ice formation, we were having a very difficult time being able to thaw oocytes and having them survive.

That all changed in the last few years with rapid cooling, or vitrification. We are now able to essentially dehydrate the egg completely and rapidly cool at a rate of minus 30,000 Celsius per minute. So we're taking it from room temperature to minus 196,000 within seconds. OK?

What this does is it freezes it in a glass-like state. All right? There was no time for ice formation. You just dunk it, essentially, in liquid nitrogen after exposure to high concentrations of cryoprotectants.

And this is what happens. So this is the starting oocyte. And as you expose to cryoprotectants, this is what it looks like. And you rapidly freeze. It doesn't look so good. But when you go back and thaw it, because you've frozen it in a glass-like state, you can actually rapidly reverse, and it resumes its normal morphology.

Because of vitrification, vitrification essentially changed the game of how we freeze embryos and oocytes now. So it's no longer considered experimental. Because of high post-thaw survival rates, fertilization and pregnancy rates are actually similar to IVF in young patients. In older patients, implantation rates might be a little bit compromised, but again, not significantly so.

There are some challenges that we face in patients who are undergoing controlled ovarian stimulation. And the first one is time. Right? We see these patients. The oncologist wants to start chemotherapy as soon as possible. We need at least two weeks of just when we start hormones on these patients to get to egg retrieval. And normally in a patient, when I start them on ovarian stimulation, I would have to prep them with birth control pills for at least three weeks, or Lupron, and then start them.

This is what a typical calendar looks like. So you you're looking at a period of at least three weeks at minimum, five to six weeks maximum because we're very menstrual cycle dependent. Right? So we have to wait until the patient has a period. And then we're trying to mimic the menstrual cycle. It can be time-consuming for sure.

So how do we bypass that? A newer technique over the last few years has been reported. And it's called random start ovarian stimulation where you essentially start these patients at the moment they present to us to prevent delay. So essentially what we would do is we would administer them a GnRH antagonist, stop any brain hormone production, cause lysis of whatever egg they're making that month or whatever, if they're post-ovulatory, the corpus luteum. And then once we're in control, once the estrogen has dropped, we're in control of the cycle again, and we can start them on hormonal stimulation.

So a study by Kim and colleagues actually showed that the total oocyte number was actually higher in random start patients the number of mature eggs were also higher in random start patients. And the oocyte maturity rate was higher in random start patients.

And this is what it just essentially looks like. So if a patient presents to us on day 10 of her cycle, we would just start her on GnRH antagonist, continue it until her estradiol level drops, and then start her on gonadotropins. Continue gonadotropins for a period of 10 to 12 days until follicles look mature. And then go and retrieve those oocytes. Same thing if they present in the luteal phase.

Another challenge that we have in breast cancer patients that we don't necessarily in hematologic oncology patients is they're estrogen sensitive. We're driving their estradiol levels up 10 to 15 times the normal amount. Right? So peak estradiol levels in a natural cycle is anywhere from 200 to 400 picograms per millimeter. We're talking about estradiol levels of 1,500 and above. So certainly not advantageous for patients who have this kind of malignancy.

So how do we bypass that? And there's multiple strategies for this that have been studied. One is just natural cycle IVF. Patients that are ovulatory are going to make one to two eggs a month. You just wait for them to grow those eggs, and then you go and aspirate them. All right?

The second one is the realization of tamoxifen, which is a SERM. Obviously, it increases endogenous FSH and LH levels. And so it's in endogenous stimulation for the patient. So you may make more than one egg like you would in a natural cycle. And then lastly, and the most promising, is controlled ovarian stimulation with the use of concurrent aromatase inhibitors.

Just briefly touching on natural cycle IVF. Again, your peak estradiol levels are what you would normally have in an ovulatory cycle. It can take approximately two to four weeks for retrieval because we're completely dependent on patient cycle and completely dependent on her making her own eggs. Another disadvantage is poor oocyte yield. So just because a patient has an egg that you were even able to retrieve doesn't mean that it's mature. And you can only fertilized mature eggs. So there's a high cancellation rate as a result of that.

Tamoxifen cycles do a little bit better than natural cycle. Mature oocyte yields may be higher compared to natural cycle. And if you actually use tamoxifen with low dose gonadotropins, you can increase that oocyte yield even more compared to tamoxifen alone. So in one study, they reported 5.1 versus 1.5.

And now, this is the new gold standard. So Kutluk Oktay and his colleagues reported a controlled ovarian stimulation protocol whereby you just start the patients on a low dose letrozole right before you start them on ovarian stimulation with gonadotropins. You stop it at the time of trigger, and then you restart it after egg retrieval again to drive those hormone levels back down. He called it the COST-LESS protocol, which is Controlled Ovarian Stimulation with Letrozole Supplementation.

And what he found was that it significantly lowered peak estradiol levels compared to standard IVF. So he took patients that were undergoing the COST-LESS protocol and then compared them with just standard patients who were undergoing IVF for tubal factor infertility and compared their characteristics and found that peak estradiol levels were significantly lower in the COST-LESS protocol compared to a normal cycling patient. Some studies report that it may be even lower than that.

Another advantage was there was a 44% reduction in gonadotropin requirements and treatment costs because the Femara is actually driving up endogenous gonadotropin production so you don't have to give them as many exogenous gonadotropins.

And here were some more characteristics. And they actually found that once again, estradiol at the time of ACG trigger were significantly lower. And there were no differences in total oocytes, mature oocytes, and fertilization rates. And what they found was total FSH dose, which is exogenous gonadotropins, was significantly lower. So helpful to these patients that are already undergoing very expensive treatment, and then to have to ask them to undergo a cycle of IVF can be very cost prohibitive. So it certainly helps.

That's all well and good. But how safe is it? So the same authors actually followed 215 women. 79 had undergone treatment with the COST-LESS protocol. And 136 patients with breast cancer did not undergo any form of controlled ovarian stimulation, and went straight to treatment. And they found, for obvious reasons, that the time lapse between surgery and chemotherapy was significantly longer in the controlled ovarian stimulation group-- to be expected. The median follow up was 10 months less in the COS group compared to the control group. And what they found was there was no significant difference in relapse-free survival between the groups in the time that the patients were followed. All right? So of course, they weren't followed for a prolonged amount of time, but approximately two years, and there were no significant differences.

Why could that be? So we have to interpret these data with some care because why did those patients-- this was a prospective study. Why did those patients that did not undergo stimulation, why did they not undergo it? Well, it may be that they had more aggressive breast cancers and the oncologist did not feel comfortable with them undergoing it. So there's a significant confounder there.

Another thing that is a very real problem with these type of stimulation protocols is ovarian hyperstimulation. Just across the board, 5% of all of our patients that are undergoing this for fertility will have this syndrome. And with breast cancer patients or any cancer patients, we are limited with time. So going low and slow with their gonadotropins is not an option a lot of times because I don't have the leisure of being able to stimulate them for two to three weeks. Right? We have to get them in, get them out, so they can start their chemotherapy.

So HCG is an agent which is what usually causes ovarian hyperstimulation when we administer it for final oocyte maturity. So Oktay and colleagues actually attempted a GnRH agonist trigger, so Lupron to make the patient mount their own LH surge. So instead of using HCG to trigger oocyte maturity, we would use Lupron to mount an LH surge.

And what we found-- or what they found, not we, were there were no differences in total oocytes. Mature oocytes were actually higher in the GnRH agonist trigger. Maturation rates were higher. Fertilization rates were higher. And this is the most important statistic here. 10 people in this group of 47 had severe hyperstimulation syndrome compared to just one in the treatment group.

There are certain experimental modalities that I'm just going to briefly touch on. And one of them-- I get asked about this all the time-- is should we be using GnRH agonists for fertility preservation. Right? It's controversial. The literature shows that it probably is not very efficacious. However, it may be efficacious for prevention of premature ovarian insufficiency.

So the skeptics say that it actually doesn't physiologically make sense for it to do anything because the follicles that we're trying to preserve are resting follicles that are not hormonally responsive. We know patients who've had SH receptor mutations are able to recruit these follicles just fine. So it's a completely hormonally independent process. So what good does taking away hormones do? Proponents state that it may actually be direct effects to the ovary, such as reducing ovarian blood flow.

This is a systematic review that was published by Clowse et al. in 2009. And it shows that there is no definitive evidence that GnRH agonist administration helps for fertility preservation. So this is specifically looking at infertility as an endpoint.

I was able to pull three studies from there, however, that specifically looked at patients with breast cancer. And the metric they were studying was looking at premature ovarian insufficiency. And they found that administration of GnRH agonists routinely across the board decreased risk of premature ovarian insufficiency.

Again, we have to interpret these data with care because look at this study over here. They only followed patients from three to eight months. You can't even really diagnose premature ovarian failure until a patient has been amenorrheic for at least 12 months. So just because a patient hasn't had menses in three months, I mean, you really can't-- you have to be very careful with interpreting these data.

Ovarian tissue banking has been utilized now for numerous cases of hematologic malignancies. So there's broader implications because just a small piece of cortex gives you a lot more follicles than you would ever get with controlled ovarian stimulation. So you would essentially remove the cortex, freeze it with vitrification, and then either retransplant it at a later time at a pelvic site or an extra-pelvic site, or in vitro, try to mature some of those follicles.

So 24 live births have actually been reported with retransplanting that ovarian tissue at a pelvic site. It has not worked at extra-pelvic sites. So some studies have actually tried to put the ovarian tissue back underneath the dermis and then stimulate them with IVF and then do a transdermal oocyte retrieval and then make embryos and put it back in. That has not worked for obvious reasons.

And this is what it looks like. So this is a patient who's had an oophorectomy. You would just take a small piece of the cortex out and then cut it up into small pieces and then freeze with rapid vitrification.

Just a brief blurb about our center. We recently became a Live Strong Center for Excellence for Fertility Preservation, which we are so proud of, because what that means is our patients are able to qualify for free medications. So the cost of gonadotropins can run up to \$4,000 to \$5,000 in addition to the normal cost of an IVF cycle. It's very cost prohibitive for a lot of patients. And so the fact that they're able to qualify for free medications is huge.

To conclude, discussion is key in a multi-disciplinary approach to the breast cancer patient. Not being able to possibly conceive after chemotherapy in a reproductive age women really can be emotionally devastating if having a child has always been her dream. Early referral is recommended if a patient is interested in pursuing embryo or oocyte cryopreservation. Embryo or oocyte cryopreservation are still the gold standard. But I would encourage people to actually consider use of GnRH agonists if either controlled ovarian stimulation is time restrictive and the patient can't do it because she has an aggressive breast cancer or if it's a cost prohibitive. Other modalities are still experimental.

And these are my references. Thank you.