So I'm going to start the seminar by discussing the effects of chemotherapy on gonadal function. So as you’re all aware almost 140,000 Americans of reproductive age are diagnosed with cancer annually. And somewhere between 30-75% of men and 40%-80% of women in this group face the risk of infertility because of their treatment. Because we’re getting so much more sophisticated with our ability to diagnose and treat cancer along with this increased survivorship and risk for infertility, there is certainly a growing interest in expanding reproductive options for these patients.

So what do we know about female fertility and how cancer treatment can affect female fertility? What we know is that women are born with a finite pool of eggs and although this has been challenged by one group in Boston over the last decade, this is still certain the dogma that’s held in reproductive endocrine and infertility. We also know that cancer treatment can certainly affect this pool of eggs.

So before we talk about this effect I think it’s critical to review 2 very basic concepts about ovarian physiology and I’m not going to review the menstrual cycle but the first basic concept is that in the human adult female ovary there’s 2 pools of follicles. The first pool is this primordial pool I hope you guys can see this. The primordial pool of eggs or the non-growing follicle pool. This is what women are born with and this is what will ultimately determine their reproductive potential through life. The second pool is the growing follicle pool and in fact there are waves of follicles that are recruited from this non-growing follicle pool even before sexual maturity is achieved. And after sexual maturity, one dominant follicle emerges it will ultimately undergo several maturation steps leading to the expulsion of a mature oocyte around the time of ovulation.
The other important concept is what happens to that egg through the maturation process because the cell cycle and stage will really tell us how sensitive these cells are to the mutagenic effects of chemotherapy. So these primordial follicles or that non-growing follicle pool, the eggs within those follicles are rested in a prolonged diplotene phase of meiosis I and they are still in that phase when they get initially recruited into the growing follicle phase. It’s the lead follicle that will ultimately expulse a mature egg after the luteinizing hormone surge, so that egg will finish meiosis I, enter meiosis II and be arrested in the metaphase stage of meiosis II until fertilization happens, and the length of time that it takes for a follicle or an egg to really achieve full maturity is about 6 months.

So what then happens to that pool of eggs as a woman ages? This is perhaps my favorite depiction of what happens to that non-growing follicle pool and this was a model that was derived from 8 quantitative histologic studies using over 325 female specimens. And to orient you on the Y axis is that non-growing follicle population based on those histologic, the samples. And on the X axis is age. To the right of zero is in years, the left of zero is in months. What we see is clear, that that rate of decline or the number of non-growing follicles certainly does decline as we get older. The number of non-growing follicles is greatest in utero and even before birth there’s a slight decline. The rate of decline starts to elevate or increase as early as the early thirties and this becomes more precipitous in the late thirties, around 37 ultimately culminating in menopause which on average in a Caucasian patient population in the U.S. is 51. But I think a more interesting way to look at this data and what the authors of that paper, what the primary objective of that paper was, was to estimate what percent of that non-growing follicle pool remains at different ages. So this curve represents
that 95th percentile of what we would expect is left as we get older. So a thirty year old woman would have approximately 10% of that non-growing follicle pool remaining and the woman who is 40 has less than 5%. This is a great illustration of why age is such an important determining factor for how chemotherapy can affect gonadal function. Certainly in older women with a smaller non-growing follicle population will have a greater chance of premature ovarian failure following chemotherapy or any type of cancer treatment.

Chemotherapy can also have both direct and indirect effects on the follicle and the ovary. The direct effects are mainly through apoptotic pathways activation of CA and P63 pathways, that’s the primary mediator of chemo induced ______ apoptosis in human ovarian follicles. And indirect effects are mainly through vascular compromise. So when you look at histologic specimens of ovaries that have been exposed to chemotherapy there’s thickening and hyalinization of cortical vessels and ultimately that leads to cortical fibrosis. Now it’s important because the cortex is really where the non-growing follicle population lives.

So how do we categorize risk? I think there’s 3 really important counseling points to make when talking to a patient about how chemo or cancer treatment could affect fertility. The first is that the effective chemo on the ovary isn’t an all or none phenomenon and that’s really because in many young patients with a very large non-growing follicle pool, ovarian damage is often partial. But it doesn’t mean that that patient isn’t at risk for subfertility or premature menopause in the future. In fact the return of regular menstrual cycle is often a poor surrogate for fertility because that can happen because of the larger non-growing follicle pool.
Having said that although it’s a poor surrogate marker for fertility the usual or typical outcome that we will get in most of the literature, and in general we categorize chemotherapy as falling into one of three risk zones. High risk cancer treatments are those that in more than 80% of patients premature ovarian failure or cessation of menses will occur at the completion of treatment. Intermediate risk cancer treatments 30%-70% will have a cessation of menses and lowest treatments, less than 20% will have a cessation of menses. Certainly multi-agent chemotherapy regimens it’s very difficult to predict ultimate outcome and you have to individualize that risk assessment based on other factors that could predict subfertility in the future like smoking or BMI. But there are certainly some regimens, multi-agent regimens that have consistently been shown to fall into one of these 3 risk categories.

As I mentioned before age is certainly a very important determining factor. For example, in women with pre-menopausal breast cancer, if the same chemotherapy agent is used in someone over 40 more than half may undergo premature ovarian failure versus less than 30% and usually less than 20% in women under the age of 35. And of course dose, recurrence needing multiple cycles of chemotherapy will have a cumulative effect.

So the impact of chemotherapy is dependent on survival or loss of that non-growing follicle pool. The short term effects during treatment are really temporary amenorrhea and that’s a result of destruction of those growing follicles. On average time to resumption of menses following any intermediate risk chemotherapy can usually be that time that we expect for an egg to reach maturity,
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SHWETA NAYAK, MD, FACOG

so somewhere between 5 and 7 months. The long term effect however is what we’re truly interested in because this is represented by a loss of that non-growing follicle pool that will ultimately lead to either subfertility or premature ovarian failure.

So ultimately what do we think happens after cancer treatment or exposure to chemotherapy in a woman, likely a shortened fertility window and potentially an advanced age at which menopause occurs. So we know women are born with a finite pool of eggs and cancer treatment can certainly affect that pool.

So what about men? Men are entirely different because spermatogenesis is extraordinarily productive and men produce millions of sperm each day. Cancer treatments can damage the spermatogonia or stem cells that make sperm resulting in long term or permanent infertility. This is a depiction of spermatogenesis in the male. It actually takes about 12 weeks for sperm to be fully mature from the time that they’re created from the spermatogonial stem cells in the testicle. These rapidly dividing differentiating stem cells are much more sensitive to killing by radiation and nearly all chemotherapy from the later aged sperm that’s maturing. The eventual recovery of sperm really depends on the survival of those stem cells, their ability to regenerate their numbers, and their ability to further differentiate and mature.

Similar to partial ovarian depletion, moderate doses can induce partial stem cell killing. This can produce azoospermia that can last longer than the expected 12 weeks that it takes to achieve maturity. But the kinetics of recovery can be much more delayed and often more than 2 years.
So what types of treatment can affect azoospermia or male fertility? With single dose radiation therapy that kinetic change, meaning recovery, can be anywhere from more than 21 weeks to up to 2 years and 15% of men who receive more than 10 gray of testicular radiation they may have permanent azoospermia. Fractionated radiation therapy can cause greater delay in spermatogenic recovery and lower total doses are required to achieve total azoospermia.

The highest chance for recovery after chemotherapy is really within the first years and if we don’t see sperm in a semen analysis by 5 years it’s pretty rare for them to have any recovery at all. Very similar to females the main culprit for chemotherapy that can cause the greatest risk for azoospermia is alkylating agents.

So in females cancer treatments lead to a shortened fertility window and earlier age at menopause and mechanisms for chemo induced ovarian damage can include apoptosis as well as indirect effects from cortical fibrosis.

In males cancer treatment can alter sperm kinetics leading to either permanent azoospermia or subfertility.