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Southeastern Fertility Center Perspectives

About Southeastern Fertility Center

Southeastern Fertility Center, founded in 1982, is home to the first IVF conception and birth in South Carolina. Since the first IVF baby was born in 1985, the team at SEFC has also introduced blastocyst transfer, frozen embryo transfers, micromanipulation techniques, genetic testing, oocyte tissue cryopreservation and an active donor oocyte program. Grant W. Patton Jr. MD, John A. Schnorr MD and Michael Slowey MD are dedicated to providing the most personalized, effective treatment available for couples who are experiencing infertility. In addition to clinical expertise, SEFC also offers the IntegraMed® Attain IVF® Refund Program which was developed to reduce a couple's financial anxiety by fixing the costs associated with multiple IVF cycles. SEFC has offices in Mt. Pleasant, Columbia, and Myrtle Beach along with additional monitoring sites in Savannah and Wilmington, to conveniently serve patients across the region. To learn more about SEFC, visit www.sefertility.com.

Breast Cancer in Young Women and It's Impact on Reproduction

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Breast cancer is the most common cancer in women in developed countries with the incidence unfortunately increasing in younger women. In fact, 12% of all breast cancers occur in women 20-34 years of age. With survival from breast cancer significantly improved over the past decade, the potential late effects of treatment of their breast cancer can have a significant impact on the quality of life of these young women. Accordingly, young women are more likely than older women to have questions regarding the potential side effects of therapy including the risks of infertility, recurrent pregnancy loss, premature ovarian failure, and the impact of a pregnancy on their breast cancer.

Level 1 evidence from large randomized controlled trials demonstrate equal survival rates with breast conserving therapy and radiation therapy versus mastectomy in patients with early breast cancer. Systemic adjuvant therapy, including hormonal therapy and/or cytotoxic chemotherapy, is used in conjunction with surgery with the aim of eradicating micro-metastasis. A variety of different



chemotherapy regimens are utilized and all are thought to have varying degrees of harmful effects to ovarian function. The alkylating agents are considered the worst in regards to future ovarian function. The ultimate impact of chemotherapy

on a woman's reproductive function is thought to be related to a woman's underlying age. The younger she is, the more refractory her ovaries are from chemotherapy. Additional parameters to consider include the type of the drug being used, the dose of the drug, duration of use, and the status of ovarian function prior to its use.

Common effects of chemotherapy on ovarian function include infertility,

temporary amenorrhea, and menopause. Amenorrhea rates following a cycle of Ifosfamide use range from 21-71% in women less than 40 years of

age, and from 40-100% in older women.

A rule of thumb is that chemotherapy used for breast cancer appears to add about 10 years of ovarian age in terms of reproductive function. Unfortunately, many young women are not fully aware or well informed of the potential adverse repro-



ductive functions of chemotherapy. We have several options to offer patients with newly diagnosed breast cancers facing chemotherapy treatment. Perhaps the simplest option is to offer Depo-Lupron in advance of chemotherapy administration. Until recently, we only had retrospective studies on the role of GnRH agonists prior to chemotherapy. This fortunately changed with the prospective randomized study published in *Fertility and Sterility* by Badawy et. al. in January 2009 which randomized 80 patients with breast cancer to chemotherapy with or without Lupron treatment. In summary, the study group which received the GnRH analog had 89.6% of patients resume menses and 69.2% resuming ovulation within eight months after chemotherapy, and the patients receiving chemotherapy without Lupron, only 33.3% resumed menses and 26.5% had normal ovulatory ovarian activity. Median FSH and LH concentrations were also reduced showing an increased number of follicles within the ovary for those patients on treatment with Lupron compared with patients not treated with Lupron. There also may be benefit in regards to breast cancer survival with Lupron treatment. In my mind, this is a minimum that should be done for patients receiving chemotherapy desiring reproductive function in the future.

Additional options are available through the use of assisted reproductive technologies. These can be controversial and require individualized discussions and recommendations. Both options include ovarian stimulation with exogenous gonadotropins which result in the development of multiple follicles and elevated estradiol levels. In theory, these elevated estradiol levels could stimulate residual breast cancer and worsen the patient's outcome. This has yet to be proven and given the very short period of time the estrogen is elevated, it is thought to be extremely unlikely to alter a patient's prognosis. Following the brief ovarian stimulation, GnRH antagonists can be used to prevent ovulation, thereby shortening the treatment approach. The retrieved eggs can then be used for individual oocyte cryopreservation or embryo cryopreservation.

In regards to oocyte cryopreservation, this is a clearly up-and-coming technology which has been the focus of a significant

amount of research. Using the latest vitrification techniques for individual oocytes both at Southeastern Fertility Center and other centers, egg survival following the thaw is approximately 90% with fertilization rates of 70-75% and blastocyst development of 40-50%. Several publications show reasonable pregnancy rates of

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approximately 30% per treatment cycle for women under 35 years of age at the time of their oocyte cryopreservation.

A second option for women who have a partner would be to fertilize the retrieved eggs with sperm resulting in embryos which can be cryopreserved.

We have been able to cryopreserve embryos as an industry for over 20 years now with high success rates. Embryo survival rates from frozen embryos are approximately 75% with clinical pregnancy rates for women under 35 years of age with a cumulative pregnancy rate of approximately 60%.

Other technologies, such as cryopreservation of unstimulated ovarian tissue which is resected prior to chemotherapy, have continued. The results show sporadic pregnancies reported around the world; however, this appears to be a very research-oriented proposal, which in my mind is dwarfed by the increasing success found with individual oocyte cryopreservation. One of the disadvantages of ovarian tissue cryopreservation is that subsequent transplantation could result in the transmission of an unrecognized ovarian metastasis back into a cured patient.

In summary, breast cancer is unfortunately all too common. Fortunately, however, survival rates have increased significantly in breast cancer patients requiring us to focus on the long term effects of the treatment. For younger patients we need to focus on maintaining ovarian function and reproductive function. I feel that it is imperative that we counsel patients regarding the reproductive options prior to the administration of chemotherapy and at a minimum discuss with them the possible benefit of Depo-Lupron prior to and during their chemotherapy. I look forward to hearing your thoughts on this subject. *Please do not hesitate to email me at schnorr@mus.edu.*

Fertility After Cancer for Men

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Dr. Schnorr has presented an excellent overview of what we can do for breast cancer patients. This basic paradigm is similar to how we look at all of our female patients who are dealing with or have survived cancer. But in South Carolina, cancer has a much higher incidence (586 vs. 391 per 100,000) and death rate (270 vs. 161 per 100,000) in men than it does in women. Thus, we frequently need to deal with men who have survived cancer. The most common types of cancer in "reproductive age" men are Hodgkin's disease and Testicular cancer. Life-saving cancer treatments can reduce fertility by damaging or destroying gametes, limiting gamete development,



damaging (or having removed) part or all of the reproductive tract and altering the overall health of the individual. But Hodgkin's disease and Testicular Cancer may also have a direct impact on the germinal epithelium through cancer

related malnutrition, tumor-related hypermetabolism and immune response to the cancers (anti-sperm antibodies, cytokines). Men have an inherent advantage over women in that sperm development is continuous throughout a man's life after puberty, due to stem cells able to provide new gametes even after significant insults. But this cannot be taken for granted: Schmidt et al had 82% of 67 male cancer

patients opt to cryopreserve sperm. Out of that group, only 43% had any motile sperm after treatment.

So what can we do to preserve fertility for men about to be treated for cancer? Fertility preservation can be thought of in three stages: before treatment, during treatment, after treatment.

Before Cancer Treatment. When a young person is diagnosed with cancer, survival tends to be the primary concern. The literature demonstrates that nearly 80% of women would like information regarding the impact of their diagnosis and treatment on fertility. But men are also interested, as 77% of men who were childless at time of diagnosis desired to preserve their fertility. The hallmark of treatment at this stage is cryopreservation of existing sperm. It is important to remember that the most likely use of this sperm will ultimately be in vitro fertilization. This is for several reasons. First, individuals with chronic illnesses often have compromised gamete formation, and thus, the specimen quality could preclude its use for insemination to begin with. Rueffer et al demonstrated that 70% of their patients to be treated for Hodgkin's disease had abnormalities on their pre-treatment semen analyses. Second, intrauterine insemination using cryopreserved sperm from cancer patients is not particularly effective. Good cryopreserved sperm has reduced pregnancy rates of ~ 15% per cycle (versus 25 % per cycle in normal couples with fresh sperm). Typical pregnancy rates seen are similar to those published by Subiak et al, with cancer survivors having only 5% per cycle IUI pregnancy rates. Thirdly, there are a variety of other factors that can significantly affect IUI outcome including the female partner's age, and other existing infertility factors. Thus, it would take a number of cycles to achieve success, if it were to occur at all. When one takes into account that most couples desire more than one child, it is unlikely that a young man can produce enough specimens in the time constraints prior to treatment to make IUI viable for one pregnancy, let alone create the desired family size.

We recommend that the young man produce as many specimens for cryopreservation as possible in the time allowed. There should be no regard given to the time between ejaculations. Although the "ideal"



specimen for semen analysis is obtained after 2-5 days of abstinence, we are simply trying to collect as much sperm as possible. One well-designed study suggested that although the concentration will diminish with increased frequency of ejaculation, it usually remains in the normal range for normal men. Further, men with a variety of abnormalities on the semen analysis do not see much change with increased ejaculatory frequency.

During Treatment. The primary mechanism for damage to gamete formation for both radiation and chemotherapy is through apoptosis. As we all know, these treatments work best on rapidly dividing cells, making the developing spermatocytes prime targets. A method that has been looked at for over 20 years, but is now just gaining wider acceptance in women, is the use of a GnRH analog during treatment. In men, the down-regulation of the pituitary will remove the trophic hormones for sperm development, theoretically leaving them less susceptible to damage. Unfortunately, only one of 8 clinical trials to date has demonstrated an advantage in men. The drug of choice should be Lupron, since it comes in a depot form that is given every 30d and is the most potent agonist available. Fortunately, the side effects profile is minimal in men. At this time, it should be used only after extensive counseling regarding known literature or part of an IRB-approved protocol. It takes about 7-10 days for the Lupron to take effect, but should be started ASAP once specimens have been

collected for cryopreservation.

After Treatment. Once a given therapy has been completed, it is reasonable to wait 2-3 sperm cycles (74d/cycle) to see if there are any sperm being produced. Where you go from there, depends on the results. In some treatments (antibiotics, antimetabolites, plant derivatives, immune interventions) only temporary reductions occur and recovery can be good. This could mean that no further intervention may be needed for a couple. If the specimens are moderately to severely compromised, and the couple does not desire to wait to see if there is further recovery, then in vitro fertilization will be needed to effectively utilize the sperm. Significant radiation (> 3-4 Gy), alkylating agents and platinum analogs are likely to produce prolonged, if not permanent, azospermia. This being said, recovery to some degree can occur 2-5 years out from treatment. If no sperm is available from a fresh ejaculate in the time-frame desired for family building, then the cryopreserved sperm is brought into play. The cryopreserved sperm will be most efficiently used through in vitro fertilization because of the small amounts usually available, and the small amount needed to accomplish IVF using ICSI for insemination. Of course, if no sperm is available at all from the individual, the use of cryopreserved donor sperm from a registered sperm bank can be easily obtained and used in a variety of ways for family building.

This year, there will be over 1.4 million new cancers diagnosed in the United States, with about a third of them occurring in men in an age group that can impact family building. The excellent care provided by our oncologists and surgeons means that these men have increased survival and improved prognosis. However, these life-saving treatments can have a profound impact on the reproductive potential of the survivors. In men, sperm cryopreservation is an easy and effective means of providing for family building in the future should the cancer treatments render them sterile. Whenever possible, these and other options should be discussed with the patient before their cancer treatment.

**References available upon request.*

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SC's First IVF Baby Turns 25 and Celebrates at Southeastern Fertility Center's Baby Reunion Party



Southeastern Fertility Center celebrates the state's first baby born with the help of In-vitro Fertilization (IVF). Morgan Meece turns 25 this November 20th, and celebrated along with other miracle babies and their families at Southeastern Fertility Center's baby reunion party at Alhambra Hall in Mt. Pleasant, September 27th. All of the children who attended the party, including Morgan, have one critical thing in common; they were brought into this world with the help of fertility treatments at Southeastern Fertility Center.

Southeastern has been successfully helping couples conceive through treatments, including In-Vitro Fertilization (IVF), for twenty five years. The Baby Reunion Party, held every two years, gives these families a chance to celebrate and reunite with the team at Southeastern Fertility Center, while also having the opportunity to meet other couples who used Southeastern to build their families. The party offered little ones and their parents a memorable fall carnival with clowns, games, treats and lots of fun.

Employees at the Center were thrilled to spend this year's event with Morgan. Southeastern's President and Founder, Dr. Grant W. Patton, Jr. said, "I can't wait to see Morgan again, she was the first successful IVF baby in the entire state and I'm honored to have performed the procedure that brought her into this world, She truly is a miracle."

In addition to achieving the first IVF birth in 1985, the Southeastern team has also completed the first Gamete Intrafallopian Transfer (GIFT) and Zygote Intrafallopian Transfer (ZIFT) pregnancies in South Carolina and have introduced blastocyst embryo transfer, frozen embryo transfers, intracytoplasmic sperm injection (ICSI), pre-implantation genetic diagnosis and most recently oocyte cryopreservation (egg freezing).

If you are new to the area and would like information on our services, please contact Narda Ray-Hentges at (843) 819-3434 or narda.ray-hentges@integrated.com