Chapter 12
Fertility in Cancer Survivors

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Introduction

Individuals undergoing treatment for cancer may be at risk of treatment-related infertility depending on their type of cancer and treatment modalities utilized. Cancer treatments can damage gonadal tissue, gametes or sex hormones [1, 2]. Ovarian tissue is susceptible to damage during chemotherapy, radiation or surgery. Ovarian damage from chemotherapy is drug and dose dependent and related to the age at the time of cancer treatment. There is a higher risk of infertility and premature ovarian insufficiency in older women who receive, for instance, alkylating agents with a high CED. By one estimate, the typical chemotherapy protocol can result in depletion of 10 years' worth of ovarian reserve [3].

Risk of Chemotherapy and Radiation on Fertility

There are three proposed mechanisms by which chemotherapy agents are thought to lead to ovarian insufficiency or infertility. First, chemotherapeutic agents have been shown to accelerate recruitment of primordial follicles, by activating the PI3K/PTEN/Akt pathway. This leads to early activation of follicles, then a "burn out effect" of the ovarian follicle deposit [3–5]. Secondly, chemotherapeutic agents can directly damage quiescent follicles by way of DNA damage; particularly, alkylating agents and doxorubicin, both of which cross-link with DNA leading to cellular apoptosis. DNA damage-induced follicle death appears to be mediated by TAp63, a

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F. Hannah-Shmouni (ed.), *Familial Endocrine Cancer Syndromes*,
https://doi.org/10.1007/978-3-031-37275-9_12

transcription factor in the p53 family [6]. Finally, chemotherapeutic agents are thought to indirectly injure the ovary by disrupting vascularization in the ovary, and lead to fibrosis of the ovarian cortex. The pre-pubertal ovary appears to be more resistant to gonadotoxic chemotherapeutic agents, which may be due to the presence of more follicles of the absence of active folliculogenesis in this patient population [7]. The testis, and specifically primordial sperm cells, are also extremely susceptible to the toxic effects of both radiation and chemotherapy and treatment can result in oligospermia or azoospermia.

Several risk stratifying calculators have classified the gonadotoxic risk of cancer treatment into several categories: no risk, low risk (<20%), intermediate risk (21–80%), and high risk (80%) [8]. The LIVESTRONG/American Society of Clinical Oncology (ASCO) fertility risk calculator, in particular, describes the risk of amenorrhea in women. Criteria used for this risk calculator include cancer type, treatment dose and duration, age, and pubertal status. Although fertility risk calculators are frequently utilized in clinical decision-making, there are some issues to keep in mind. Risk calculators that describe the risk of amenorrhea may not accurately reflect the risk of infertility. Women who undergo chemotherapy may resume regular menstrual cycles despite significantly diminished ovarian reserve [3]. Secondly, the wide range of risk in the intermediate category (ranging from 21% to 80%) makes counseling regarding actual risk and recommendations for fertility sparing treatment more challenging. Furthermore, the LIVESTRONG risk calculator is based on cancer treatment protocols in the USA and Europe, and may not be applicable to different demographics [9].

Other risk stratification systems include the alkylating agent dose (AAD) and cyclophosphamide equivalent dose (CED). Both systems quantify the exposure to an alkylating agent such as cyclophosphamide. The AAD is based on the drug dose distribution of patients from the Childhood Cancer Survivor Study; the CED, on the other hand, is independent of this study population. A classification chart reported by Anderson et al., based on pretreatment AMH levels of women with early stage breast cancer, is meant to predict loss of ovarian function, characterized as ongoing menses or treatment-induced amenorrhea [10]. Per this chart, the resumption of spontaneous menses was seen at AMH above 20.3 pmol/L, and amenorrhea following AMH below 3.8 pmol/L. For AMH values between 3.8 and 20.3 pmol/L, an age threshold of 38.6 years predicted menses or amenorrhea. A recent study also reported on a standardized risk assessment for adolescent and young adult patients [11]. Depending on the CED, the type of chemotherapy, or radiation exposure measured in Gy, treatment-related infertility or gonadal insufficiency is categorized into "minimally increased," "significantly increased" or "high level of increased" risk [11].

Certain chemotherapeutic agents have been associated with various impacts on gonadal tissue. Alkylating agents such as cyclophosphamide or chlorambucil, known to be highly gonadotoxic, function as metabolites that cross-link with DNA, leading to inhibition of DNA synthesis and function, and subsequent apoptotic death of primordial follicles [3, 12]. Alkylating agents have an intermediate to high chance of causing infertility based on the cumulative dose that is prescribed [1].

Platinum agents, such as cisplatin and carboplatin, act by platination of DNA which is similar to alkylation and also acts to induce apoptosis [13]. Platinum-based compounds are considered to entail an "intermediate" risk of gonadotoxicity. Additionally, higher doses of chemotherapy that are used for priming for hematopoietic stem cell transplant are associated with high risk of infertility, which can often be permanent [14]. Other intermediate risk agents include anthracyclines and taxanes [1]. Another "intermediate" gonadotoxic agent is doxorubicin, which inhibits the topoisomerase II enzyme and intercalates into DNA, to impair DNA replication. This has multiple effects, including the accumulation of DNA fragments leading to cell death, as well as the production of oxygen-free radicals [3, 15]. Agents including methotrexate, 6-mercaptopurine, 5-fluorouracil, vincristine, bleomycin, and actinomycin have little or no risk of causing infertility.

Radiation to the abdomen and pelvis, in addition to total body irradiation or cranio-spinal radiation that can impact the hypothalamic pituitary gonadal axis, is associated with a high risk of infertility. Whole abdominal/pelvic radiation >15 Gy in pre-pubertal females, >10 Gy in post-pubertal females, and > 6 Gy in adults has been associated with infertility [1]. The impact of radiation on future fertility is additionally related to fractionation schedule and age at the time of radiation treatment [16].

Workup Prior to Fertility Preservation

The gonadotoxic effects of cancer treatment has raised the need for a marker that assesses ovarian reserve and can predict ovarian function after treatment. A biomarker that accomplishes both tasks is key to patient counseling regarding fertility preservation treatment options. There are a number of markers of ovarian reserve, including FSH, E2, AMH, inhibin B, ovarian volume and total AFC; of these, AMH appears to have the most potential as a biomarker to track ovarian reserve and function prior to and after cancer treatment. AMH is produced by granulosa cells of growing preantral and small antral follicles. Its value remains relatively constant over the menstrual cycle. It can also be used as a marker in adolescent patients, for whom FSH and inhibin B levels are not useful in measuring ovarian reserve. Pretreatment AMH informs the clinician about the responsiveness of the functional ovarian reserve in women planning for ovarian stimulation for gamete cryopreservation [10]. While AMH level does not reliably predict clinical outcomes such as pregnancy or live birth rate, it has been used to help determine the stimulation dose of FSH in ovarian stimulation [4].

AMH also has been shown to predict ovarian function after cancer treatment, depending on the woman's age. Studies have shown that post-treatment AMH is reduced compared to pretreatment baseline, however, the trajectory of AMH recovery after cancer treatment depends on the pretreatment level, as well as type of chemotherapy received and the woman's age [3, 10]. Specifically, cancer survivors older than 30 years of age the time of diagnosis had lower post-treatment AMH

trajectories, compared to patients under the age of 30. Pretreatment AMH has been used as part of an infertility risk calculus, as explained above [17].

There are a few caveats to keep in mind regarding the interpretation of AMH. Pretreatment AMH levels may be decreased in women with lymphoma, as well as women with *BRCA1* mutations [18, 19]. For women who receive GnRH agonist therapy during chemotherapy, post-treatment AMH levels may be suppressed as a result [20]. Further, interpretation of AMH values can be challenging in puberty, when AMH levels tend to decline in the peri-pubertal stage. Lastly, there is no standardization of commercially available assays measuring AMH, each with varying reference ranges, and inter-assay differences make direct comparisons difficult [20].

When counseling patients on fertility preservation options, it is important to discuss infertility risks and predicted post-treatment ovarian function, whether by way of risk calculators (as discussed above) or biomarkers such as AMH. Modifiable risk factors to infertility, such as tobacco or alcohol use, environmental toxin exposure and high body mass index, should also be taken into consideration. A previous history of infertility should also be noted.

Importantly, reproductive-age cancer patients should be assessed for hereditary or familial cancer syndromes, given their relatively early onset of cancer. They should be referred for genetic counseling and testing. Identification of a hereditary or familial cancer syndrome changes not only fertility preservation but also the cancer treatment regimen. For women with BRCA 1/2 or Lynch Syndrome, for instance, the recommendation for risk-reducing bilateral salpingo-oophorectomy narrows the fertility preservation options and affects the timeline for treatment. As noted above, women with BRCA mutations have been found to have lower AMH levels; it is unclear whether this suggests decreased ovarian reserve or fertility in the context of a germline mutation, however, patients should be counseled appropriately. Patients with hereditary cancer syndromes should be offered sperm or oocyte/embryo cryopreservation as the first line. This is particularly helpful because preimplantation genetic diagnosis (PGD) can be undertaken after IVF. PGD is a procedure that tests the blastomere biopsy for aneuploidy or genetic disorders, before embryo transfer. This genetic testing is particularly valuable for patients with hereditary cancer syndromes, such as BRCA1 and 2, Lynch Syndrome, familial adenomatous polyposis (FAP), Von Hippel-Lindau disease (VHL), Li-Fraumeni syndrome, multiple endocrine neoplasia (MEN) syndromes or retinoblastoma. Other techniques of prenatal diagnosis, such as chorionic villus sampling and amniocentesis, can be discussed as well.

Fertility Preservation Options in Females

If it is possible to delay cancer treatment after diagnosis, established fertility preservation procedures should be considered prior to treatment, which include oocyte cryopreservation and embryo cryopreservation (Fig. 12.1). Both procedures involve approximately 10–14 days of controlled ovarian stimulation with gonadotropins

prior to retrieval of oocytes, followed by cryopreservation of mature oocytes via slow freezing or vitrification techniques [21]. Ovarian stimulation is not feasible prior to puberty, given the inactive HPO axis in pre-pubertal girls. Since conventional ovarian stimulation is associated with high serum estrogen levels, treatment with selective estrogen receptor modulators like tamoxifen or aromatase inhibitors

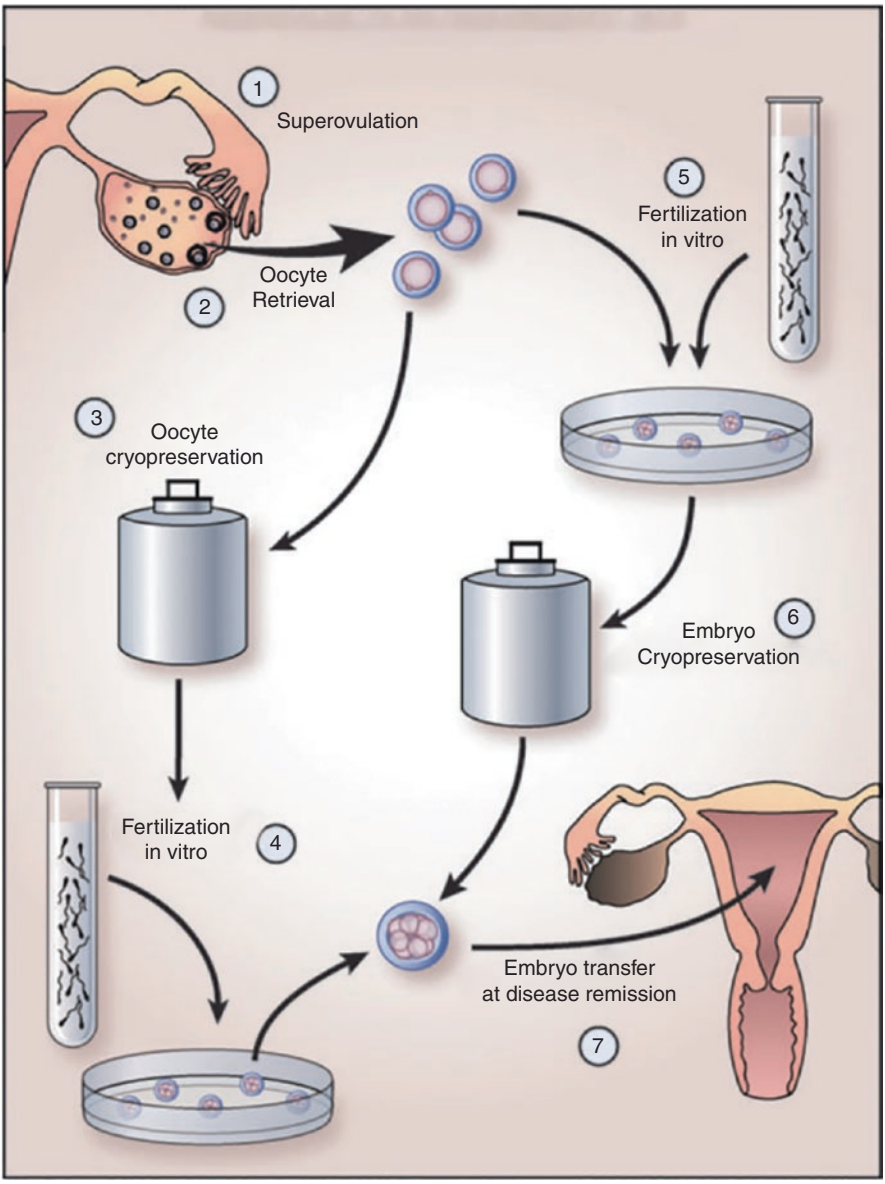

Fig. 12.1 Established fertility preservation technologies

such as letrozole, may be beneficial to keep estrogen levels low during stimulation in estrogen-sensitive cancers such as breast and endometrial cancer [22]. After oocyte retrieval, embryo cryopreservation involves fertilization of harvested oocytes with sperm via in vitro fertilization or intracytoplasmic sperm injection. Single women who are not partnered, decline sperm donation, or are opposed to embryo creation, may opt to cryopreserve oocytes as opposed to creating embryos for cryopreservation. The Italian Registry of Assisted Reproductive Technology (ART), which has compiled outcomes on 2152 live births resulting from cryopreserved oocytes, has shown no increase in rates of congenital anomalies associated with these pregnancies [23].

An experimental technique, ovarian tissue cryopreservation, involves harvesting ovarian cortical tissue, since the large majority of oocytes are located within primordial follicles in the ovarian cortex, in order to preserve fertility [24]. Ovarian tissue cryopreservation is the only fertility preservation method available for pre-pubertal patients and may be the optimal treatment for post-pubertal patients with aggressive malignancies that require immediate treatment prior to oocyte or embryo cryopreservation. This technique can also be considered in patients who cannot receive hormonal ovarian stimulation based on their cancer type. This procedure involves removal of approximately one-third to one-half of the ovary, via laparotomy or laparoscopy, with subsequent creation of thin slices of tissue (0.3–2 mm thickness) prior to cryopreservation. Before the tissue slices are cryopreserved, samples are tested to ensure no malignant cells are present within the tissue. The risk of transplanting malignant cells is an important consideration for women with known familial or hereditary cancer syndromes. Once cancer treatment is completed and the patient desires pubertal induction or fertility, the tissue is thawed and reimplanted, as an auto-graft back into the ovarian fossa or to a heterotopic site [25]. Orthotopic autotransplantation back into the pelvis allows for attempts at natural conception. Heterotopic transplantation of ovarian tissue, performed with reimplantation into the forearm, abdominal wall and chest wall, does not allow for spontaneous pregnancy but permits ovarian stimulation, oocyte retrieval and IVF using ART technologies. Following autotransplantation, ovarian function has been shown to resume between 2 and 9 months. Risks associated with ovarian tissue cryopreservation include ischemic damage to the tissue and the possibility of reimplantation of malignant cells. Autotransplantation of frozen-thawed ovarian tissue is currently contraindicated in ovarian carcinomas and leukemia given the high risk of reintroduction of malignant cells [26]. To date, approximately 120 healthy babies have been born from autotransplantation of ovarian tissue after ovarian tissue slow freezing/thawing [27]. Ovarian graft survival depends on the amount of ovarian tissue autotransplanted and the age at which the ovarian tissue was harvested. To date, the longest graft survival has been 7 years [28].

Additionally, in vitro maturation, a process by which oocytes undergo maturation in an in vitro setting, is a technique that can be utilized to obtain mature oocytes from ovarian tissue. This technique can also be used when immature oocytes are obtained from unstimulated ovaries, when utilized in pre-pubertal females or when stimulatory cycles cannot be performed due to time limiting factors or treatment

limiting factors [29, 30]. Immature oocytes are cultured for 24–48 h in order to mature into metaphase (II) oocytes that can be used for IVF or be frozen through slow freeze or vitrification processes. In vitro maturation is a promising method for patients who cannot delay gonadotoxic therapy or for whom ovarian stimulation is contraindicated [31]. Studies have demonstrated that the number of mature oocytes achieved through IVM has been shown to be associated with AMH [32]. This suggests that a patient with lower pretreatment AMH level may not achieve a sufficient number of mature oocytes after IVM.

For patients undergoing cancer treatment that has been associated with complete ovarian failure, whole ovary cryopreservation prior to treatment with subsequent slow freezing or vitrification, is an experimental technique that has been performed in both animal and human models. A fresh whole ovary transplant between a living donor and recipient has resulted in live birth, but no live births have been documented after transplantation of previously cryopreserved autologous ovaries [33]. While the majority of whole ovary cryopreservation cases have been associated with high follicular loss due to cryoinjury and vascular complications post-transplant, the inclusion of a large vascular pedicle with the removed ovary can salvage blood supply to the ovarian graft [34].

Other current experimental studies in animals have looked at utilization of the "artificial ovary," a multi-step ex-vivo process of sequential in-vitro culture of ovarian tissue, follicles and oocytes to produce mature oocytes for IVF. In a study using a murine model, preantral follicles were grown in a fibrin scaffold which functioned as the artificial ovary; the follicles were later transplanted and found to be viable in vivo [35].

Ovarian tissue culture research and stem cell research to produce oocytes are other topics of active research for fertility preservation. Recent findings have challenged the dogma that the number of oocytes in the human ovary is finite. Studies have reported the isolation of oogonial stem cells, in human ovaries as well as murine models [36, 37]. However, the role of oogonial stem cells in the lifespan of ovarian function is yet to be fully elucidated, and how stem cells can improve reproductive function remains unclear. There is currently no therapy involving oogonial stem cells in the development of human gametes.

New research has explored the use of "ferto-protectant" pharmaceutical agents that protect against chemotherapy-induced ovarian insufficiency or infertility, in the preclinical setting. A recent study showed that recombinant AMH decreased primordial follicle loss after administration of cyclophosphamide, cisplatin or doxorubicin [38]. Other pharmaceutical agents that have been studied include: sphingosine-1-phosphate (S1P), shown to help resist radiation-induced follicular apoptosis in murine models; imatinib, which blocks apoptotic pathways in primordial follicles exposed to cisplatin; AS101, shown to decrease activation of the PI3K/PTEN/Akt pathway thereby limiting early activation of primordial follicles and the "burn out effect" in rodents after cyclophosphamide treatment; G-CSF, which promotes vascularization and can counteract chemotherapy-induced ovarian vascular ischemia; tamoxifen, which may help preserve the ovarian follicle deposit, although data are conflicting; and nanoparticles to encapsulate chemotherapeutic agents to

improve delivery and limit exposure of surrounding tissue [39–43]. Other agents under investigation include crocetin, mTORC inhibitors, LH, ghrelin, and antioxidants [15].

Currently there is conflicting data on the utility of GnRH agonists in preventing primary ovarian insufficiency in cancer patients undergoing treatment by suppressing folliculogenesis [12, 22]. It has been postulated that the administration of GnRH agonists before and during chemotherapy suppresses the number of primordial follicles entering the growing pool of follicles, making them less sensitive to gonadotoxic chemotherapy. Other theories suggest that GnRH agonists may upregulate intra-ovarian anti-apoptotic molecules and protect ovarian germline stem cells [44–46]. For women with known hereditary cancer syndromes requiring risk-reducing salpingo-oophorectomy after cancer treatment, the provider may consider the use of GnRH agonists for ovarian suppression during chemotherapy [46]. Currently the National Comprehensive Cancer Network (NCCN) guidelines acknowledge use of GnRH agonists in preventing chemotherapy-induced ovarian failure in estrogen receptor negative tumors (National Comprehensive Cancer Network), however, the American Society of Clinical Oncology (ASCO) does not have recommendations regarding GnRH agonists for this indication. Additional neoadjuvant cytoprotective pharmacotherapies are currently being investigated.

To preserve fertility in patients undergoing radiation, techniques such as gonadal shielding and oophoropexy can be utilized to shield the ovaries from the detrimental effects of abdominal/pelvic radiation. Oophoropexy involves surgical transposition of the ovaries, either laterally toward the pelvic sidewall or medially behind the uterus, to move the ovaries away from the field of pelvic irradiation. The success of oophoropexy has been related to the dose, type and site of pelvic radiation, patient age and coadministration of chemotherapy [47].

Advancements in cancer treatment have additionally allowed for fertility sparing treatments that avoid surgery that would otherwise render a patient infertile. Such advancements include the hormonal management of early endometrial cancer, radical trachelectomy for cervical cancer and uterine-sparing surgery for early stage ovarian cancers.

Fertility Preservation Options in Males

The gold standard for fertility preservation in post-pubertal males involves sperm cryopreservation. Previous studies have demonstrated fertility success rates in young men (14–30 years old) utilizing previously frozen sperm is 36% for intrauterine insemination and 50% when utilizing IVF/ISCI [48]. If certain underlying medical comorbidities preclude patients from successful ejaculation, electro-ejaculation can be utilized for microsurgical testicular sperm extraction (TESE), which extracts spermatozoa from testicular tissue [49, 50]. In children, who cannot ejaculate, epididymal or testicular sperm extraction can be considered. Limited options remain available for pre-pubertal males undergoing cancer treatment, since the pre-pubertal

testis does not produce mature spermatozoa. Experimental procedures currently available include maturation of spermatogonia from testicular tissue biopsy which has been shown to be successful in animal models [51].

Ethical/Legal Considerations

There are a number of ethical issues related to fertility preservation for cancer patients. Reproductive-age cancer patients should receive counseling, even if they express no interest in future children, as many fertility preservation options also preserve ovarian endocrine function. First and foremost is the question of informed consent. Patients should be counseled thoroughly on the various fertility preservation options, as well as associated pregnancy and live birth rates. Importantly, some methods of fertility preservation are experimental or not as well established, and patients should be informed that fertility preservation aims to preserve future reproductive potential but does not ensure it [52]. Providers should also ascertain whether patients are psychologically, intellectually and emotionally competent to consent or assent to treatment. When minors are faced with cancer diagnoses, they often make decisions with their family and parents have decision-making capability when it comes to preserving their child's fertility, if the intervention is likely to provide benefit. If and when possible, it is recommended to obtain child consent. There is a consensus for a two-stage consent process: at diagnosis, then after treatment when the patient is at a developmentally appropriate age [52]. If minors openly object to treatment, fertility preservation treatments should not be performed.

Particularly for patients with known familial or hereditary cancer syndromes, they should be counseled on the importance of preimplantation genetic testing (PGT). The benefits of avoiding transfer of an affected embryo, and passing on the mutated gene, is critical for the patient's decision-making process. However, patients and their families may have religious, cultural or personal objections to PGT or embryo cryopreservation, so these issues should be addressed prior to cancer treatment if possible.

Another area of ethical concern is the disposition or posthumous use of cryopreserved gametes. Unless otherwise specified, gametes should be discarded if the child does not survive to adulthood, however, when possible, instructions regarding the disposition of gametes should be made at the time of fertility preservation [53]. The provider should also address how potential disagreements between family members regarding the posthumous use of gametes should be adjudicated. It is also helpful to ascertain the patient's wishes to donate his or her gametes or gonadal tissue to scientific research. Often a multi-disciplinary approach is taken to address potential conflicts of interest in the event of the patient's death.

Any medical decision made with an adolescent patient should be navigated carefully and with the patient's best interests in mind. The provider should determine whether the patient is an appropriate candidate for enrollment in available clinical trials, and discuss this with the patient and family. Participation in a clinical trial

may provide new opportunities for fertility preservation, however research on children and adolescent patients is strictly regulated and will require informed consent or assent. Children are a vulnerable population, and their decision-making can be easily influenced by their parents' or families' wishes [54]. The provider should advocate for the patient, and try to ensure that any decision regarding fertility preservation reflects patient autonomy and respects the opportunity for future family building, if desired. In short, all decisions should be made with the goal of providing "an open future" for the patient [53]. Lastly, all ethical considerations should be made within the legal framework.

Post-Treatment Follow-Up for Cancer Patients

Compared to healthy controls without cancer, reproductive-age cancer survivors have lower rates of post-treatment pregnancies [55]. The chances of post-treatment pregnancy depend heavily on the female patient's age at time of diagnosis, cancer treatment as well as cancer type. Post-treatment counseling may include measures of ovarian failure, which can be objectively measured through follicle-stimulating hormone, FSH, the most common biochemical marker used to assess ovarian damage or failure. Additionally, anti-mullerian hormone (AMH) and antral follicle count can be used to assess ovarian reserve post-treatment. Post-treatment AMH, compared to pretreatment baseline, may predict return of ovarian function, as discussed above.

Optimal timing for pregnancy following cancer treatment is currently unknown and largely depends on the patient's current medical status, prognosis, and possible harmful effects of therapy. The timing of attempting pregnancy should be based on shared decision-making and involve the oncologist as well as reproductive endocrinologist. Some patients attempt pregnancy 2–3 years after finishing cancer treatment, and after monitoring for possible cancer recurrence. Other patients, such as those with hormone receptor positive breast cancer, require long-term hormonal therapy after treatment. The data on the timing of pregnancy for these women, as well as the safety of pregnancy, is very limited but encouraging [55]. Planning for pregnancy should take into account the "wash-out" period needed for patients on adjuvant endocrine therapies (i.e., 3 months after discontinuing tamoxifen). The data on the safety of ART in women with hormone receptor positive cancer is also very limited; this subset of fertility preservation patients often require the use of third-party reproduction. Studies evaluating pregnancy outcomes in cancer survivors have found no increase in congenital malformations in offspring, primarily in women who have conceived spontaneously after chemotherapy [56]. However, some studies have suggested increased obstetric complications in post-treatment pregnancies, such as increased risk of premature birth, low birth weight, and need for cesarean delivery [55].

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