Preservation of gonadal function in women undergoing chemotherapy: a review of the potential role for gonadotropin-releasing hormone agonists

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A cancer diagnosis in women of reproductive age has unique medical and psychosocial ramifications, especially with treatments that are known to cause gonadal toxicity. For patients who undergo chemotherapy, a multidisciplinary team approach is essential to ensure that the patients' reproductive wishes are addressed. Currently, embryo and oocyte cryopreservation are the standard of care for those who wish to preserve their fertility. The use of gonadotropin-releasing hormone agonists has been a source of debate with numerous studies that have investigated the efficacy on both fertility and ovarian function preservation. This review evaluates the current literature on the use of gonadotropin-releasing hormone agonists for preservation of gonadal function. Assisted reproductive technology is excellent for preservation of fertility but will not protect gonadal function. Protection of gonadal function is critical for the broader issues of health and quality of life as a result of a hypogonadal state. At this moment, gonadotropin-releasing hormone agonists are the only drug class available to protect gonadal function.

Key words: chemotherapy, gonadotropin-releasing hormone, ovarian function, premature ovarian failure

Each year, approximately 35,000 women between 15 and 39 years of age are diagnosed with cancer in the United States.[1,2] Improved treatments and clinical outcomes encourage investigation to improve long-term complications and quality-of-life issues. This population has unique medical and psychosocial needs that differ from older or younger individuals with a cancer diagnosis.[2] As such, guidelines emphasize the importance of a multidisciplinary team approach to patient care.[2]

Cancer treatment is known to affect ovarian reserve negatively and impact ovarian function. Chemotherapy directly destroys ovarian follicles and accelerates the natural time-related decline in ovarian reserve.[1,3] The impact of treatment depends on patient age, baseline ovarian reserve, and chemotherapy type, dose, and duration.[2,3] Nonetheless, this effect is highly variable and difficult to predict, with some patients regaining regular menstrual cycles and exhibiting little to no long-term effects; others experience infertility and/or premature ovarian failure (POF).[1,3]

Fertility preservation remains an important and often neglected issue for women of reproductive age who are diagnosed with cancer. Particularly with the trend for reproduction at older ages, increasing numbers of cancer survivors may be interested in childbearing, and many identify infertility as a source of significant distress.[1] It is important to note that ovarian reserve relates specifically to reproductive potential, thereby necessitating a discussion of reproductive wishes before the onset of chemotherapy. Although this is undoubtedly an important issue, fertility represents only 1 component of overall gonadal function, which in turn impacts many other body systems (Table 1). Ovarian function contributes to the complete hormonal milieu of a patient, with a significant impact on well-being and quality of life. As such, chemotherapy-related POF can also have significant implications on quality of life. Symptoms facing cancer survivors may include hot flashes, insomnia, vaginal dryness, dyspareunia, anxiety, and/or mood disturbances. Patients commonly struggle with changes in sexuality; treatment-related physical and endocrine changes could impact sexual function greatly.[4] These sequelae may lead to further psychologic stress and relationship strain.[4] In addition to menopausal symptoms and sexual dysfunction, there are also systemic medical consequences of long-term estrogen deprivation, which include osteopenia/osteoporosis, cardiovascular disease, neurocognitive decline, and endocrine disorders.[5]

Mechanisms of chemotherapy-induced gonadal damage [T1]

Although the relationship between chemotherapy and decreased ovarian reserve has been well-established, the underlying mechanism is not well understood. There are multiple proposed mechanisms of how chemotherapy may exert an effect on ovarian follicles, which includes both direct and indirect pathways (Figure 1). The [F1] mechanisms may also vary depending on the specific chemotherapeutic agent used.

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TABLE 1
Sequelae of decreased ovarian function

Menopausal symptoms
Vaginal atrophy
Vasomotor symptoms
Mood disturbances
Sleep disturbances
Osteoporosis/osteopenia
Cardiovascular disease
Infertility
Neurocognitive decline
Sexuality
Depression/anxiety
Changes in skin sensation
Vaginal dryness
Dyspareunia
Decreased sex drive/libido
Associated relational distress

Hickman. GnRH agonists for preservation of ovarian function during chemotherapy. Am J Obstet Gynecol 2016.

Amenorrhea that occurs during treatment is secondary to the loss of growing follicles.[6] Chemotherapeutic agents can cause apoptosis of follicles directly, with the dividing granulosa cells being particularly susceptible to damage.[7,8] The direct loss of growing follicles causes an accelerated recruitment of primordial follicles and a decrease in the total ovarian follicular reserve. This results in a faster depletion of the primordial follicle pool and, in turn, decreased fertility.[7] The diminished reserve may manifest immediately after treatment with persistent amenorrhea or have a delayed clinical presentation with infertility or POF long term.[6] Last, changes to ovarian stromal tissue are evident after exposure to chemotherapy. Studies of ovarian tissue after chemotherapy treatment demonstrate stromal fibrosis and damage to blood vessels.[6,7] The resultant local ischemia further contributes to overall follicular depletion.

Theories that support the concomitant use of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy treatment describe ovarian protection from both the direct and indirect influences. GnRHa act at the level of the anterior pituitary, where it binds GnRH receptors. Initially, GnRHa have an agonistic effect, stimulating secretion of LH and FSH.[9] This "flare" effect is the most significant in the early follicular phase, when a large reserve of gonadotropins is present in the anterior pituitary. Prolonged activation of the receptors leads to a desensitization and disruption of GnRH pulsatility. As such, gonadotropin secretion becomes downregulated, which causes a hypogonadal state. Overtime, a loss of GnRH receptors also occurs.[9] At the ovary, GnRHa are thought to decrease vascularity, thereby reducing the concentration of chemotherapy acting directly on the ovary.[6] GnRHa have also been shown to inhibit primordial follicle recruitment, thereby attenuating the accelerated depletion of ovarian reserve and providing protection to fertility.[6,7]

Management

The impact of a cancer diagnosis on a woman of reproductive age is significant and has a potential impact on fertility, quality of life, bone health, cardiovascular disease, sexual health, and overall mortality rates. The oncologist serves a crucial role in patient education. After cancer diagnosis, the oncologist must explain the implications of cancer treatment, including the planned chemotherapeutic regimen, the potential side-effects of treatment, and the benefit of the regimen proposed, which includes the anticipated disease-free survival (Figure 2). The oncologist should also initiate a discussion on the risk of POF if a gonadotoxic regimen is planned and ensure that a referral to a reproductive endocrinologist is provided so that fertility and other concerns related to hypogonadism can be explained further to the patient. The development of a multidisciplinary treatment team is necessary for the treatment of reproductive-aged women with a malignancy.

The reproductive endocrinologist also plays an important role in the counseling of a woman with a cancer diagnosis (Figure 2). A comprehensive discussion with the patient regarding whether future fertility is desired is essential. If future fertility is desired, consideration of the cancer diagnosis and timeline for Q2 Q3 treatment may impact the options that are available to the patient. Other patient-specific features that can impact treatment options include the patient's age and ovarian reserve work up. It is important that consideration of the potential gonadotoxicity, patient's wishes, and risks/benefits of fertility preservation treatment be weighed carefully. Ovarian reserve and future fertility can be impacted even by regimens with low gonadotoxicity, and patients whose condition relapses may progress to subsequent, more gonadotoxic treatments. Patients, when appropriate, should also be counseled that they may not require assistance with conception in the future.

There are various proposed strategies for preservation of fertility and gonadal function in women who undergo cancer treatment. For fertility preservation, these include embryo, oocyte, or ovarian tissue cryopreservation (OTC) and pharmacologic ovarian suppression with GnRHa. Options are further limited for gonadal function preservation, because GnRHa and OTC are currently the main options available to address ovarian preservation and thereby endocrine function.

Embryo and oocyte cryopreservation before the initiation of chemotherapy has proved to be very successful and to date has been considered the first-line options for fertility preservation. Embryo preservation requires the use of ovarian stimulation and fertilization of [F2] embryos with either a partner or donor's sperm, which are then stored for later use. Oocyte cryopreservation is an alternative option for postpubertal girls, single women who prefer not to use donor sperm, and individuals with moral or ethical concerns regarding embryo cryopreservation. It is important to counsel patients that the pregnancy rates after oocyte cryopreservation are related to the number

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