OPINION

Fertility and fertility preservation techniques for breast cancer patients

Fouzia Memon, M.B.B.S.
Research Fellow, Newcastle upon Tyne NHS Foundation Trust, UK.

ABSTRACT

Breast cancer is not rare in younger women. There has been remarkable improvement in the survival rate due to progress in cancer treatment. Those treatments often cause premature ovarian failure due to massive destruction of the ovarian reserve. Early loss of ovarian function not only puts the patient at risk for menopause-related complications at a very young age but is also associated with loss of fertility. The purpose of this paper is to review the incidence of gonadal toxicity associated with adjuvant chemotherapy, fertility concerns, and the options to preserve fertility in young breast cancer survivors.

Key words: Breast cancer, premenopausal, reproduction, fertility preservation.

INTRODUCTION

Breast cancer is the most common female malignancy. There are 2.2 million breast cancer survivors and approximately 25-30% of newly diagnosed breast cancer patients each year are <50 year of age. Sonmez et al (2006) and Ghaoor et al (2003) found that the incidence of breast cancer has increased by 0.5% per year over the past decade, whereas the death rate has decreased by 1.4% per year during the same period (1, 2). The estimated incidence is less than 0.1 per 100,000 women below the age of 20 years, increasing to 1.4 for women 20-40 years, 8.1 for women 25-29 years and 24.8 for women 30-34 year old (3). The decline in mortality is more remarkable in women age <50 year (4). With the lower mortality and longer survival rate resulting from adjuvant therapy, chemotherapy or endocrine therapy may be recommended to women <50 year of age, depending on the stage, prognostic factors, and hormone sensitivity of the tumor. The use of adjuvant cytotoxic chemotherapy for the treatment of breast cancer can induce ovarian failure and infertility, while the use of adjuvant hormonal therapy is a contraindication to conception during therapy. Further, women in this millennium have been delaying initiation of childbearing to later in life, hence the preservation of fertility in female patients diagnosed with cancer has recently been an area of intensive investigation. This article reviews the literature, discusses the pathophysiology and effect of breast cancer treatment on fertility, chances of spontaneous pregnancy and summarizes available fertility preservation options and discusses recently published data concerning experimental methods.

The problem: gonadal damage induced by chemotherapy

Damage to the gonads by chemotherapy depends on the patient’s age at the time of treatment, total dose and nature of chemotherapy
delivered. The exact mechanism of ovarian damage is not fully understood, but in-vitro studies suggest apoptotic changes in the granulosa cells that result in follicular damage (5). Chemotherapeutic drugs used in various combinations for the treatment of breast cancer, such as three-drug combination of cyclophosphamide and fluorouracil with either methotrexate (CMF) or an anthracycin (CAF, FAC) (6). The addition of Paclitaxel (taxanes) in addition to cyclophosphamide have been shown to possibly increase gonadotoxicity (7), Although earlier on Stone in 2000 (8), Swain in 2005 (9) and Ball in 2001 (10) found that adjuvant chemotherapy in women (<45) with or without taxanes resulted in a slightly lower incidence of amenorrhea in young women. The alkylating agents such as cyclophosphamide, which can damage resting cells, is more toxic to the ovaries than cell cycle specific agents, such as methotrexate and fluorouracil, whose major effect is on ovarian follicle growth and maturation (11,12). Ovarian biopsies performed in women undergoing treatment with cyclophosphamide showed stromal fibrosis, marked reductions in the number of oocytes, and the lack of follicular maturation (13). Since the cell cycle specific agents damage growing follicles therefore sex steroid production is interrupted, which may lead to disturbance of the hypothalamic-pituitary-ovarian axis, with eventual irregular menses, amenorrhea, and menopausal symptoms. In the absence of ovarian production of estradiol, feedback inhibition on the pituitary is lost and follicle stimulating hormone (FSH) levels rise to menopausal levels. Follicle stimulating hormone levels are frequently used to assess ovarian failure and ovarian reserve in women who have abnormal menses or amenorrhea after receiving chemotherapy. Most of the data pertaining to the likelihood of having amenorrhea with adjuvant chemotherapy for early breast cancer from women having cyclophosphamide, methotrexate, 5-fluorouracil (CMF) and these results may not be directly comparable to anthracycline-based chemotherapy regimens. In the MD Andersen hospital and tumor institute series, no patient Less than 30 years of age treated with a doxorubicin-containing regimen stopped menstruating compared with 33% of patients aged 30-39 years and 96% of those aged 40-49 years (14).

Tamoxifen, a selective estrogen modulator with antiestrogenic actions on breast tissue, is an important part of the adjuvant therapy for early-stage, hormone-sensitive breast cancer. In addition to symptoms associated with the hormonal changes of induced menopause due to antiestrogenic effects, endocrine therapy is also associated with a variety of other symptoms, that include vasomotor symptoms, vaginal complaints (dryness, itching, discharge), amenorrhea, insomnia, and mood disturbances (15). Adjuvant therapy with tamoxifen do not cause permanent amenorrhea, but tamoxifen treatment can last up to 5 years, during which pregnancy is contraindicated. (16).

Spontaneous pregnancy after chemotherapy

Overall, at least half of women under 35 years of age resume menses at some time after completion of chemotherapy (17, 18). On the flip side, resumption of menstruation after chemotherapy does not mean that fertility has been preserved. Studies are not available which assess actual fertility since they require longer follow-up, determination of premorbid fertility, and determination of the percentage of patients who attempt conception. In one study evaluating 119 women aged 35 years or younger who had been treated with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) there were 33 pregnancies among 25 women who either continued or resumed menstruating (21%). The median age of those who became pregnant were 28 years (range 22-33), and the median interval between the last chemotherapy treatment and pregnancy was 12 months (Range 0-87). The overall reproductive potential of this group of women could not be assessed, since no attempt was made to determine what percentage of the menstruating women attempted conception or used contraception. Of the 33 pregnancies there were 10 elective abortions, two spontaneous abortions, 19 full term pregnancies and two women were pregnant at the time of the report. There were no preterm deliveries and no fetal abnormalities among the 19 live offspring (18).
Fertility preservation strategies

There is a recognized need to discuss fertility and options to preserve fertility before adjuvant chemotherapy for young women with breast cancer. Surveys of cancer patients reveal a very strong desire to be informed of available options for fertility preservation and future reproduction (19). The desire for biologic motherhood and a genetically related child is an important issue for many cancer survivors. In breast cancer, many clinicians recommend that women should wait to consider pregnancy for 2-3 years after completion of cancer treatment because of the highest risk for early recurrence in these years. The decision will depend on the patient’s medical status and prognosis, her partner status, her age, whether reproduction can safely occur for patient and reproductive options available to them. The management of the gonadal toxicity of adjuvant chemotherapy for breast cancer is complex. It is important to consider the possibility of preventing ovarian toxicity and the therapeutic options available if infertility occurs.

Potential options for fertility preservation include cryopreservation of mature oocytes, embryo cryopreservation following in-vitro fertilization (IVF) and ovarian tissue cryopreservation (20, 21). To date the most effective approach is embryo cryopreservation, because the human embryo is the most resistant to damage caused by cryopreservation. This method requires in vitro fertilization and a male partner (22). However, cryopreservation of embryos or mature oocytes is frequently not a feasible option for reasons that include the unknown risk of the hormonal stimulation required for oocyte harvest and the inherent delay in starting chemotherapy. Cryopreservation of oocytes is not a clear option because of poor outcomes related to cryodamage of the oocyte in the process, arrested embryonic development, and increased chromosomal abnormalities in fertilized cryo-preserved oocytes. The exceptionally low pregnancy rate does not justify the use of this option for routine clinical practice. The overall published live birth rate per cryopreserved oocyte is seldom-greater than 1% to 5% (23) which is much lower than with IVF using fresh oocytes. It has been postulated that suppression of germ cell stimulation may lead to the protection of oocytes and ovarian follicles from toxic effects of chemotherapy. Although preliminary data about using gonadotropins —releasing hormone agonists concomitantly with the chemotherapy suggest that ovarian protection may be possible (24), there have been contradictory results regarding their use also (25). Many clinical trials using oral contraceptives or GnRH antagonists to suppress ovarian function during chemotherapy have had disappointing results (26). One possible reason for the lack of protection by GnRH analogue may be that the need for timely treatment of the cancer does not allow for the complete suppression of the ovarian germinal epithelium. The use of oral contraceptives prior to, or during adjuvant chemotherapy for breast cancer may stimulate growth of occult micro metastases. Other considerations include potentially increasing the risk of venous thrombosis that is seen in women receiving adjuvant chemotherapy for breast cancer and blockage of pituitary releasing factors that may result in reflex stimulation of ovarian oestrogen production (27).

There has been recent interest in banking ovarian tissue (22), rather than oocytes alone, with auto grafting of the stored tissue following chemotherapy. This technique, too, requires further investigation before it can be recommended to patients. It is anticipated that ovarian tissue will be thawed and implanted after cancer treatment as an auto graft or to a heterotrophic site or that technique for maturing oocytes in vitro will be developed in the future. With ovulation and creation of a human embryo from ovarian tissue transplanted to the arm and live birth from a antil ogous ovarian transplant already reported (22, 28), further successes in the future are likely. In July 2005, a case report was published of a successful pregnancy and birth in a woman with a history of non-Hodgkin’s lymphoma using transplantation cryopreserved ovarian tissue and in-vitro fertilization (29) although according to the authors they cannot rule out that the egg came from the native ovary rather than transplanted.
tissue, however the patient’s 24 month history of amenorrhea after chemotherapy and hormonal profile argue that the fertilization was related to the transplanted tissue.

For women who are infertile following chemotherapy, reproductive choices remain limited. In a step forward researchers from United Kingdom have successfully generated primitive sperm cells from human bone marrow derived stem cells (30). Although the use of such gamete is currently illegal in United Kingdom; such work offers the hope that derived oocytes and sperms may yet be possible. Finally for breast cancer survivors who rendered menopausal or with severely damaged ovaries following treatment adoption or childlessness may still be considered. There remains however the possibility of egg donation, which through the IVF process can offer excellent chances of a successful pregnancy.

CONCLUSION

The diagnosis of breast cancer can be devastating to young patients who desire future fertility. This review identifies the physical damage the breast cancer treatment has on young breast cancer survivors. Breast cancer chemotherapy especially alkylating agents cause destruction of primordial follicles resulting in reversible amenorrhea, irregular menses, or irreversible amenorrhea (ovarian failure-menopause). Younger women have a lower risk for amenorrhea with chemotherapy because of good ovarian reserve, although the gonadal toxicity may result in an earlier than expected menopause. The standard therapy for breast cancer treatment often result in sterility either temporary or permanent. The chances of spontaneous pregnancy still exist after cancer treatment, although a bit reduced. Currently there is uncertainty over the most effective and appropriate strategies for preserving and/or restoring an individual’s fertility. There are several considerations of fertility preservation for women who are interested in having biological child after a diagnosis of breast cancer. The decisions of whether to resort to fertility preservation and which method to use depend on a number of factors including patient’s age, the type of adjuvant therapy, and the time available before chemotherapy and the length of delay to childbearing post chemotherapy. The most recognized option for fertility preservation at present is embryo freezing.

To conclude, knowledge of pathways by which chemotherapy causes injury to reproductive function may help in the development of treatment strategies for reproductive organ protection as well as fertility preservation techniques. The improvements of these techniques as well as better characterization of their success rates and risks await further investigations.

Summary box 1

Recognized methods of fertility preservation
* Embryo cryopreservation following in-vitro fertilization
* Oocyte cryopreservation

Experimental methods of fertility preservation
* Ovarian tissue banking
* Hormonal manipulation e.g. GnRH analogue, GnRH antagonists or oral contraceptive pills.

Future strategies
* Gamete formation from human stem cells
REFERENCES


13. Hortobagyi GN, Buzdar AU, Marcus CE, and Smith TL. Immediate and long term of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D.Anderson Hospital and tumor institute. NCL Monogr 1986; 1, 105-109.


