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CLINICAL TRIALS (MN DICKLER, SECTION EDITOR)

Utility of GnRH-Agonists for Fertility Preservation in Women with Operable Breast Cancer: Is It Protective?

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Abstract Breast cancer is the most common type of malignancy in reproductive-age women. Breast cancer chemotherapy is associated with premature ovarian failure, infertility, and negative psychosocial effects related to these reproductive changes. As a result of this, fertility preservation becomes highly critical in this group of women. Besides the fertility preservation methods that utilize assisted reproductive technologies such as embryo, oocyte, and ovarian tissue cryopreservation, another suggested strategy for fertility preservation is suppression of ovarian ovulatory function by gonadotropin-releasing hormone agonist (GnRHa) administration before and during chemotherapy. However, both the efficacy and safety of GnRH agonists for prevention of ovarian damage are unproven and the preponderance of evidence indicates that this is an ineffective strategy. This review details the most recent information and studies on this controversial topic.

Keywords Fertility preservation · Gonadal suppression · GnRH agonist · Breast cancer · Chemotherapy · Gonadal damage · Clinical trials

Introduction

In the United States, an estimated 232,340 cases of new invasive breast cancer will be diagnosed in females in 2013, accounting for 29 % of all new cancer cases among women. Furthermore, the incidence rates of breast cancer for the most recent 5 years of data (2005 – 2009) remained relatively stable after decreasing by 2 % per year from 1999 to 2005 [1]. It should be noted that among all women diagnosed with breast cancer, approximately 7 % are diagnosed before the age of 40 years, being the most common type of cancer diagnosed in reproductive-age women [2].

Meanwhile, the death rates for all cancers combined, which includes breast cancer, decreased by 1.5 % per year in females during the most recent 5 years of data (2005 – 2009). The decrease in deaths rates for female breast cancer reflects the remarkable screening, diagnostic, and therapeutic advances in the practice of oncology [1].

However, as patients with these malignancies become long-term survivors, many must confront not only the temporary, but also the permanent alterations in gonadal function that are now recognized as among the most prevalent long-term side effects of cancer therapy (Fig. 1). Cancer treatments in young women may cause premature ovarian failure, infertility, and negative psychosocial effects related to these reproductive changes. In a systematic review investigating the effects of breast cancer and its treatments, particularly in young breast cancer survivors, measures of quality of life and depressive symptoms were found to be more frequent or severe in breast cancer survivors diagnosed before the age of 50 years compared with the overall age-matched population of healthy women or to breast cancer survivors diagnosed in an older age (>50 years). Concerns about premature ovarian failure and infertility were common in younger breast cancer survivors and had a role in the level of distress after treatment [3].

Because of the increasing awareness of the importance of fertility preservation, the American Society of Clinical Oncology [4•] and the American Society for Reproductive Medicine [5] have developed guidelines about this topic. Even when there is ambiguous interest by the patient, these guidelines encourage referral to fertility preservation specialists by those who provide care to young people with cancer as early in the process as possible.

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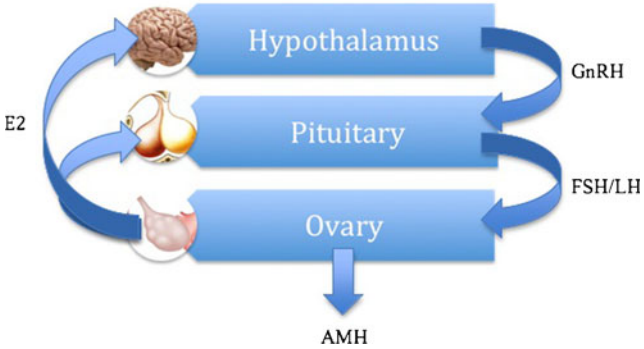

Fig. 1 The hypothalamic-pituitary-gonadal axis. The secretion of gonadotropin-releasing hormone (GnRH) from cells in the hypothalamus stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and secretion from the pituitary gland. These in turn control follicular recruitment and estrogen (E2) production at the gonadal level. Feedback of sex steroids occurs at both the pituitary and hypothalamic levels. Antimüllerian hormone (AMH) derives from early stage developing follicles and is the best current marker of ovarian reserve. The studies that utilized AMH as an ovarian reserve marker did not show any benefit from ovarian suppression in protecting ovarian reserve against chemotherapy damage [41••, 42]

Breast Cancer Treatments and Ovarian Damage

The ovaries are adversely affected by single or multi-agent chemotherapy regimens, and the magnitude of this effect is related to the age of the patient at time of treatment and the type, dose, and intensity of chemotherapy.

The age-related difference is most likely to be due to the reduction of the primordial follicle pool with aging, with an increase in the risk of developing ovarian failure and infertility in older women after a cytotoxic treatment, even at smaller doses, especially in patients at the age of 40 and older.

According to data on gonadal toxicity, chemotherapy agents of the alkylating group, such as cyclophosphamide, appear to have more profound toxic effects in the ovary and are, therefore, associated with the highest risk of infertility [6]. Of note, cyclophosphamide based regimens such as doxorubicin (A), cyclophosphamide (C), and paclitaxel (T; often referred to as AC-T); cyclophosphamide, methotrexate, and fluorouracil (CMF); doxorubicin and cyclophosphamide (AC); and docetaxel plus cyclophosphamide (TC) are commonly used in adjuvant treatment of breast cancer. All of these regimens are associated with a significant risk of premature ovarian failure and infertility [7].

Because the human ovary is relatively inaccessible to biopsy, clinical studies on the gonadotoxic effects of chemotherapeutic agents in women are generally inferred from a variety of surrogate markers, including the incidence of amenorrhea (both acute and chronic) and resumption of menses as measures of ovarian failure and preserved ovarian function, respectively. Acute amenorrhea is common during chemotherapy and results from loss of the growing follicle population. However, as long as a sufficient population of primordial follicles remains intact after completion of treatment, they will then renew the pool of growing follicles within 3–6 months. As a result, after a period of 3–6 months of amenorrhea women may resume menstruation, particularly those who are youngest at the time of treatment. Although resumption of menstruation is often considered a sign of reproductive health, it should not be associated with intact ovarian reserve. In fact, many women may experience infertility after cancer treatment because of diminished ovarian reserve, despite the resumption of menstrual cycles [8]. Further clinical research evaluating the role of ovarian reserve markers such as follicle stimulating hormone (FSH), estradiol (E2), and antimüllerian hormone (AMH), in the assessment of the impact of cancer therapy and its relationship with long-term fertility rates and pregnancy outcomes are still needed.

The mechanism of chemotherapy-induced ovarian damage is not fully understood. Because the true impact and mechanism of chemotherapy-induced damage to ovarian reserve cannot be practically determined from clinical studies, we developed a human ovarian xenograft model to address this question. This model enabled us to characterize the mechanism of action of gonadal damage induced by chemotherapy agents via histological and molecular assays. We found that, both cyclophosphamide [9] and doxorubicin [10] are significantly damaging to ovarian reserve by apoptotic follicle death and ovarian microvascular damage. The apoptotic follicle death is the result of the double strand DNA breaks caused by the actions of alkylating agent and topoisomerase inhibitors [10, 11•].

In addition to the chemotherapy-induced ovarian damage, for premenopausal women with estrogen receptor-positive breast cancer, treatment for 5 years with adjuvant tamoxifen is indicated as it substantially reduces the recurrence and mortality rates. Due to the increased teratogenicity risks, the FDA has classified tamoxifen as a pregnancy category D medication, and pregnancy should be avoided during treatment and for a 2 month period after the completion of treatment [12]. Furthermore, a recent study including women with ER-positive breast cancer showed that continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality [13•]. This delay to attempt childbearing can result in the further decline in ovarian reserve due to aging.

Fertility Preservation Options in Breast Cancer Women

The options for fertility preservation in female breast cancer patients vary depending upon the patient's age, the time available, and whether she has a partner.

Embryo cryopreservation is the most established technique for fertility preservation, and has been successfully applied to breast cancer patients [14]. It requires a male partner unless the woman is willing to consider donor sperm. It also requires

sufficient amount of time before chemotherapy treatment. Breast cancer patients are currently the largest group who can benefit from fertility preservation by embryo cryopreservation. For these women a 4- to 6-week interval between surgery and chemotherapy is adequate for ovarian stimulation and oocyte retrieval. Ovarian stimulation protocols using aromatase inhibitors in combination with gonadotropins have been shown to be effective and safe for breast cancer patients, at least in the short term follow-up [15]. The same number of oocytes and embryos were obtained compared with conventional ovarian stimulation protocols with reduced gonadotropin requirement (cost-effective approach) and reduced estrogen exposure [16]. Random start ovarian stimulation initiated in the luteal phase appeared to be successful for the purpose of emergency fertility preservation and reduces the wait period before initiating ovarian stimulation for fertility preservation [17, 18].

Oocyte cryopreservation is an option for women without a partner or who prefer not to use donor sperm. Similar to embryo cryopreservation, this technique also requires around 2 weeks of time for ovarian stimulation and oocyte retrieval. The introduction of a new cryopreservation technique, named vitrification, has improved significantly the success rates for this procedure, which is no longer considered experimental by the American Society of Reproductive Medicine [19].

Cryopreservation of ovarian tissue is considered an experimental technique for fertility preservation and is the only option available, other than in vitro maturation, for breast cancer patients who cannot delay the start of chemotherapy, such as in cases of women who will receive neoadjuvant chemotherapy. The age of the patient should be taken into account, because the ovarian reserve is age-dependent, and the procedure should not be offered to women of advanced reproductive age [20].

One of the suggested strategies for fertility preservation is suppression of ovarian ovulatory function by gonadotropin-releasing hormone agonist (GnRHa) administration before and during chemotherapy. However, both the efficacy and safety of GnRH agonists for prevention of ovarian damage are controversial.

Ovarian Suppression for Fertility Preservation: What is the Rationale?

The use of GnRHa to suppress ovarian function and therefore to reduce ovarian damage caused by gonadotoxic chemotherapy agents has been an active area of investigation. The interest in this possible protective effect of GnRHa administration arose from studies that suggested that primordial germ cells in resting follicles could be more resistant to gonadotoxic chemotherapy than germ cells in growing follicles. In fact, previous animal research demonstrated that GnRHa administration appeared to protect male mice from gonadal damage caused by cyclophosphamide [21]. In addition, an observational long-term follow-up study of children treated with chemotherapy for Hodgkin's disease showed that prepubertal administration of chemotherapy agents causes less ovarian damage compared with similarly treated adult patients [22]. Thus, it was suggested that GnRHa could exert a protective role by creating a temporary "prepubertal" state in women of reproductive age.

Suppression of the pituitary-ovarian axis and prevention of the increased recruitment of primordial follicles by the increased FSH concentration induced through the apoptosis of growing follicles is one of the proposed mechanisms of gonadal protection [23]. Additional mechanisms of protection have been proposed, such as decreased in utero-ovarian perfusion [24], activation of GnRHa receptors on ovary with decrease in apoptosis [25], and upregulation of an intragonadal antiapoptotic molecule such as sphingosine-1-phosphate (S1P) [26].

However, human studies have reported discordant findings of GnRHa efficacy and the biologic plausibility of such mechanisms has been questioned. First, primordial follicles do not express FSH or luteinizing hormone (LH) receptors, hence the recruitment of primordial follicles appears to be gonadotropin independent [27]. Furthermore, GnRHa cannot induce an acute hypoestrogenic state able to reduce the exposure of the ovaries to the chemotherapeutic agents [28]. Also, it remains unknown if GnRH receptors are expressed as a full-length, properly processed, and functional gene transcript in human primordial follicles and thus may not exhibit the same response as in animal studies [29]. On the other hand, an important safety issue has to be considered, seeing that GnRH receptors are expressed by a variety of cancers and mediate several effects, such as inhibition of apoptosis in tumor cells [30]. It is possible that GnRHa would reduce the efficacy of chemotherapy. Finally there is no such evidence that GnRHa can upregulate S1P [31].

Clinical Studies Evaluating Gonadal Suppression

The efficacy of GnRHa for prevention of chemotherapy-induced gonadal damage is controversial. There is a lack of well-designed prospective randomized controlled trials (RCTs) that have assessed the role of GnRHa administration for fertility preservation (Table 1). In the majority of the studies, the main outcome was not the long-term fertility rates and pregnancy outcomes but rather the resumption of menses, which should not be associated with intact ovarian function.

A randomized controlled trial published in 2009, limited by the small sample size and short follow-up period, reported a potential benefit of GnRHa administration on resumption of menses and spontaneous ovulation. However, significant methodological flaws limited this study and the authors did not

Table 1 Selected randomized controlled trials evaluating the use of GnRHa before and during chemotherapy in breast cancer patients

Study (y)	Participants	Intervention	Main outcome	Findings
Badawy, 2009 [32]	80 premenopausal women (<40 y) with breast cancer	Goserelin co-treatment during cyclophosphamide based chemotherapy.	Return of spontaneous menstruation and ovulation. Hormonal changes during and after the course of treatment.	The use of goserelin during chemotherapy in these patients protects ovarian function.[a]
Leonard 2010 [39] (preliminary report)	227 premenopausal women with breast cancer	Goserelin co-treatment during cyclophosphamide and/or anthracycline chemotherapy.	Incidence of premature ovarian failure.	No difference in menstruation resumption rates.
Gerber 2011 [36•]	60 premenopausal women (<46 y) with hormone-insensitive breast cancer	Goserelin co-treatment during anthracycline / cyclophosphamide-based (with or without taxane) chemotherapy.	Resumption of menses at 6 mo after end of chemotherapy.	No difference in menstruation resumption rates
Del Mastro 2011 [38]	281 premenopausal women with stage I through stage III breast cancer	Triptorelin co-treatment during different regimens of chemotherapy.	Incidence of early menopause at 12 mo after the last cycle of chemotherapy.	The use of triptorelin during chemotherapy in these patients reduced the occurrence of early menopause. *
Munster 2012 [40•]	49 premenopausal women (≤44 y) with breast cancer	Triptorelin co-treatment during cyclophosphamide-based chemotherapy.	Resumption of menses and changes in hormonal markers.	No difference in menstruation resumption rates / FSH, Inhibin A and B levels correlated with menstrual status.
Elgindy 2013 [41••]	100 premenopausal women (18–40 y) with hormone-insensitive breast cancer	GnRH analogue (Triptorelin with or without GnRH antagonist) co-treatment during cyclophosphamide-based chemotherapy.	Resumption of menses at 12 mo after end of chemotherapy and change in hormonal and ultrasound markers.	No differences in menstruation resumption rates / No differences in FSH, LH, E2, and AMH levels and antral follicle count.

[a] Important limitations were highlighted in the "Clinical Studies Evaluating Gonadal Suppression" section

AMH

consider the possible estrogenic effects of adjuvant tamoxifen treatment on the hormonal status of the patients [32].

A Cochrane review [33] and a systematic review and meta-analysis [34] also emphasized the potential benefit of GnRHa administration with chemotherapy. The Cochrane review concluded that intramuscular or subcutaneous, but not intranasal, administration of GnRHa appears to be effective in protecting the ovaries in terms of menstruation and ovulation after chemotherapy. However, no evidence for protection of fertility was found. Furthermore, this review included only 4 RCTs, the largest one being the study previously criticized [32] and the other 3 studies only contributed with a small number of patients. At the same time, the systematic review and meta-analysis published by Bedaiwy et al [34], which included 6 RCTs, also concluded that the incidence of women with spontaneous menstruation and ovulation was higher in patients who received GnRHa. However, GnRHa administration was not associated with a statistically significant difference in the rate of spontaneous pregnancy after chemotherapy. Furthermore, this study not only included the criticized trial [32], but also the short 6-month follow-up of the ZORO trial [35], which revealed relevant confounding factors, such as the younger age and the lower number of chemotherapy cycles administered in the patients in the GnRHa group, which could have overstated any advantageous outcome noted in the patients who received GnRHa. The authors of the ZORO trial recently published the 24-month follow-up [36•] and not only showed no difference in the maintenance of menstruation but also found no difference in pregnancy rates between women receiving GnRHa and the control group.

It is worth mentioning that when data from the 24-month follow-up of the ZORO trial [36•] is included and the controversial study [32] is excluded from the Bedaiwy meta-analysis [34], GnRHa use does not have a significant beneficial effect on resumption of menses or fertility [37••].

The largest RCT evaluating the use of GnRHa ovarian suppression during chemotherapy, including 281 patients, reported that the group that used triptorelin to suppress ovarian function had a lower prevalence of early menopause. However, important limitations should be highlighted such as older age of patients, use of different regimens of chemotherapy, short follow-up period, inclusion of both hormone-positive (majority of patients), and negative breast cancer patients, and lack of adjustment for tamoxifen use [38].

In contrast, other RCTs did not show a benefit from agonist co-treatment. The preliminary results of the OPTION trial [39] showed no difference in the rate of resumption of menses between patients randomized to receive chemotherapy with goserelin or controls. In another trial [40•], patients were randomized to receive chemotherapy alone or in combination with goserelin. Similar rates of amenorrhea, time of resumption of menses, and hormone levels were found between the groups. Although this trial was stopped for futility after the inclusion of only 49 of 124 patients planned, this study had several strengths, including the long period of follow-up, the use of strict criteria for the definition of amenorrhea and return of menstruation, stratification of patients by age, estrogen receptor status, and tamoxifen use. The most recent RCT evaluating the protective effects of GnRHa co-treatment also found no benefit [41••]. In this trial, all women included had hormone-insensitive breast cancer and, therefore, did not receive tamoxifen, were younger than 40 years, and received the same chemotherapy regimen. The co-treatment with triptorelin did not result in statistically significant differences in menstruation resumption rates or hormonal and ultrasound markers.

Antimüllerian hormone (AMH) is the only ovarian reserve marker that is directly produced from early stage developing follicles. Because of this, it is the best current marker to assess ovarian reserve. In the only studies that AMH was also used as a marker GnRHa did not protect ovarian reserve. One of these studies was by Elgindy [41••] as was discussed above. The other study was performed in lymphoma patients by the German Hodgkin Study Group [42]. Elgindy et al [41••] also compared another relatively sensitive ovarian reserve biomarker, antral follicle count by ovarian ultrasound. Based on that marker as well, there were no differences between the controls and GnRHa-co-treated women.

Recommendations

The American Society of Clinical Oncology guideline [4•] does not endorse the use of GnRHa as a method for fertility preservation. On the other hand, GnRHa may be used to prevent menorrhagia in women at risk for severe chemotherapy-induced thrombocytopenia and/or anemia. The patients should be advised about side effects, which include hot flashes, vaginal dryness, and bone loss. In cases where established options are not available, providers may consider GnRHa as an unproven option (preferably as a part of a research protocol).

Conclusions

Women diagnosed with cancer are interested in preserving fertility. Physicians should discuss with patients the risk of infertility and possible interventions to preserve fertility before treatment starts. Early referral to reproductive specialists can be useful, since the most established fertility preservation techniques embryo and oocyte cryopreservation require sufficient amount of time before chemotherapy initiation. Currently, there is insufficient evidence regarding the effectiveness of GnRHa, and further data establishing the safety and long-term efficacy in preserving fertility are needed.

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Compliance with Ethics Guidelines

Conflict of Interest Giuliano Bedoschi declares that he has no conflicts of interest. Volkan Turan declares that he has no conflicts of interest. Kutluk Oktay declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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