Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

Dana-Farber Breast Oncology Center

Consensus Statement Regarding Use of Ovarian Function Suppression and Estradiol Monitoring in Early-Stage Estrogen Receptor Positive Breast Cancer

Consensus: Obtained at Breast Oncology Center meetings on 06/29/2022, 02/08/2023, 05/23/2025, and 08/15/2025.

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Contents

Synopsis

Consensus Statement Regarding Use of Ovarian Function Suppression and Estradiol Monitoring in Early-Stage Estrogen Receptor Positive Breast Cancer

Clinical Question	Consensus Statement
Q1: Who needs ovarian function suppression (OFS)?	Women who are premenopausal at diagnosis are candidates for ovarian function suppression. Those who have had a period within 12 months are considered premenopausal. Menstrual function is often not evaluable, for instance in women with prior hysterectomy and for those who use certain methods of contraception including oral contraceptive pills and progesterone-releasing IUDs. In those situations, FSH and estradiol levels should be checked. If not consistent with menopause, the patient should be considered premenopausal. Patients who were premenopausal at diagnosis and have since completed chemotherapy are also candidates to receive OFS, particularly if they are going to receive oral endocrine therapy with an aromatase inhibitor (AI). Gonadotropin-releasing hormone agonist (GnRHa) use following chemotherapy is recommended for women who are reasonably likely to have resumption of ovarian function and/or are at sufficient risk of recurrence such that the harms of GnRHa injections are outweighed by the benefits of preventing resumption of ovarian function. If GnRHa use is not planned following chemotherapy in women with chemotherapy-related amenorrhea (CRA), estradiol levels should be monitored closely for resumption of ovarian function if partnering with an AI.
Q2. What is the appropriate GnRHa timing and dose?	The recommended initial dosing for leuprolide (Lupron®) every 4 weeks (q4 weeks) is 3.75 mg and for q12 weeks is 11.25 mg. For women age ≤40, we recommend q4 week GnRHa dosing, particularly for those on an AI, but can offer the option of q12 week dosing for those prefer it. We recommend the option of q4 week or q12 week dosing for women age >40. Higher dosing (Lupron 7.5 mg q4 weeks or 22.5 mg q12 weeks) is appropriate if preferred by insurance or insufficient OFS on the lower dose.
Q3. What is considered adequate suppression; when should estradiol +/- FSH be monitored; how long does it take to achieve ovarian suppression?	Ovarian suppression is usually accomplished within 4 weeks of first GnRHa injection. A postmenopausal estradiol level (<10 pg/ml using the Mayo liquid chromatography tandem mass spectrometry [LC-MS] assay) is consistent with ovarian suppression on both OFS/tamoxifen and OFS/AI and is considered adequate ovarian suppression. We suggest monitoring estradiol 3 and 12 months after initiation of OFS plus AI. Annual monitoring thereafter may be considered. FSH levels can be checked along with estradiol, and

	should be considered in situations where there is breakthrough ovarian function or when estradiol levels remain elevated despite modifications of GnRHa but a specific cutoff is not used to determine breakthrough ovarian function. We do not recommend monitoring estradiol levels for women on tamoxifen.
Q4. What should be done if breakthrough ovarian function occurs?	Breakthrough ovarian function, defined as vaginal bleeding or an estradiol level above the postmenopausal range, can be addressed by increasing the dose of the GnRHa and/or increasing the frequency of administration, though there are no available data supporting the efficacy of this practice, and limited available data do not demonstrate that breakthrough ovarian function on GnRHa is associated with worse breast cancer outcomes. Depending upon the clinical scenario and patient preferences, switching from an AI to tamoxifen until full ovarian suppression can be achieved should be considered. If there is a low degree of estradiol elevation (10-20 pg/ml) without symptoms of breakthrough ovarian function, it is reasonable to continue the current GnRHa dose and repeat an estradiol level 4 weeks later.

Introduction

Ovarian function suppression (OFS) is an important treatment for premenopausal women with early and advanced estrogen receptor positive (ER+) breast cancer. The strategic manipulation of ovarian function aims to reduce estrogen production, thereby depriving ER+ cancer cells of the estrogen required for their growth and proliferation. In the SOFT/TEXT trials, the addition of OFS to tamoxifen was associated with a 4.3% improvement in disease-free survival and a 1.8% improvement in overall survival.[1] Benefits are not uniform – women with higher risk breast cancer and women diagnosed at a very young age appear to gain more benefit from OFS.[1,2]

While OFS has been adopted as an important strategy for many premenopausal women with ER+ breast cancer, there is a notable lack of consensus within the medical community regarding its optimal management. There currently is no consensus regarding the best agent, dose, and frequency of administration to suppress ovarian function, or optimal monitoring strategies to ensure suppression in patients with early-stage breast cancer.

OFS is most commonly achieved through the use of gonadotropin-releasing hormone agonist (GnRHa) injections, such as goserelin 3.6mg (Zoladex®) q4 weeks, leuprolide 3.75 mg (Lupron®) q4 weeks or triptorelin 3.75 mg q4 weeks. Depot formulations are also available with q12 week dosing. Ovarian function suppression may also be accomplished with bilateral oophorectomy, which is a permanent and complete form of OFS. Medical OFS is often favored over surgical OFS because it is reversible. In the SOFT/TEXT trials, a 5-year duration of OFS was studied.[1] While extended OFS is sometimes recommended in clinical practice, it is generally not continued indefinitely for premenopausal women with early ER+ breast cancer. Therefore, the reversibility of GnRH agonists is advantageous. Use of GnRH agonists is also less invasive than oophorectomy and does not require interruption

of other targeted therapies, such as adjuvant CDK4/6 inhibitors. For women who plan indefinite OFS, such as those with metastatic ER+ breast cancer, oophorectomy may be preferred, particularly after a period of GnRHa exposure with good tolerability. Similarly, women who are likely to become menopausal during the duration of OFS may choose to undergo oophorectomy to obviate the need for routine injections.

Triptorelin, dosed at 3.75 mg monthly, was the GnRHa used in the SOFT trial,[1] whereas goserelin 3.6 mg monthly was used in the ASTRRA trial.[3] The EBCTCG overview[4] included mostly studies with triptorelin and goserelin, with only one of the included studies utilizing leuprolide.

Development of the Consensus Statements

The Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held multidisciplinary meetings on 06/29/2022, 02/08/2023, 05/23/2025, and 08/15/2025 to discuss recommendations for the use of OFS and estradiol monitoring in early-stage ER positive breast cancer. Clinical trial data from SOFT, SOFT-EST,[5] ASTRRA, and the EBCTCG overview, along with additional data from recent cohort studies by Lin *et al.*[6] and Tesch *et al.*[7] were reviewed. Additional relevant data were reviewed to address the questions in this document as noted below. The gathered evidence was presented for discussion to a multidisciplinary group, which included Dana-Farber physicians, nurses, clinical investigators, translational researchers, administrators, and patient advocates. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in August of 2025.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position, and overall must be considered as a consensus based on the available data, experience and clinical judgment of the Dana-Farber faculty and staff.

Clinical Questions

This document summarizes the discussions and consensus among the Dana-Farber BOC group regarding the following clinical questions:

- **Q1:** Who needs ovarian function suppression (OFS)?
- **Q2:** What is the appropriate GnRHa dose and timing?
- **Q3**: What is considered adequate suppression; when should we check estradiol +/- FSH; how long does it take to achieve ovarian suppression?
- **Q4:** What should be done if breakthrough ovarian function occurs?

Additional Considerations
This consensus does not aim to determine which patients are more likely to derive clinical benefit from ovarian suppression but instead aims to identify how ovarian suppression should be accomplished and monitored.

1. Who needs ovarian function suppression (OFS)?

Women who have had a menstrual period within 12 months and/or who have follicle stimulating hormone (FSH)/estradiol not consistent with menopause are candidates for ovarian function suppression. GnRHa use is reasonable for premenopausal women who have completed chemotherapy, even those who are 50 years or older, particularly if they are going to receive an aromatase inhibitor (AI). The APPEL trial evaluated rates of ovarian function recovery for premenopausal women (median age 48 years at baseline) following chemotherapy for early breast cancer subsequently treated with an AI. Of 45 participants, 13 (29%) developed resumption of ovarian function after chemotherapy. The median age of those who experienced recovery of ovarian function was 43 years and the median age of those who did not experience recovery was 49 years.[8] GnRHa use following chemotherapy is recommended for women who are reasonably likely to have resumption of ovarian function and/or are at sufficient risk of recurrence such that the harms of GnRHa injections are outweighed by the benefits of preventing resumption of ovarian function. If GnRHa use is not planned following chemotherapy, estradiol levels should be monitored closely for resumption of ovarian function.

Once a patient has started ovarian function suppression with a GnRHa, it is not possible to assess menopause status. While it is ok to discontinue ovarian suppression at age 60, since that also defines menopause, we do not recommend discontinuing the GnRHa with the assumption that natural menopause will have occurred after a given period, particularly for patients on aromatase inhibitors. However, if it is likely that the patient would have gone through menopause (received cytotoxic chemotherapy and in mid-50's) and the patient prefers to stop ovarian function suppression, we recommend close monitoring of estradiol levels upon cessation of the GnRHa for at least a year (3 months and 12 months) when partnered with an AI.

Consensus Statement

Women who are premenopausal at diagnosis are candidates for ovarian function suppression. Those who have had a period within 12 months are considered premenopausal. Menstrual function is often not evaluable, for instance in women with prior hysterectomy and for those who use certain methods of contraception including oral contraceptive pills and progesterone-releasing IUDs. In those situations, FSH and estradiol levels should be checked. If not consistent with menopause, the patient should be considered premenopausal.

Patients who were premenopausal at diagnosis and have since completed chemotherapy are also candidates to receive OFS, particularly if they are going to receive oral endocrine therapy with an aromatase inhibitor (AI).

Gonadotropin-releasing hormone agonist (GnRHa) use following chemotherapy is recommended for women who are reasonably likely to have resumption of ovarian function and/or are at sufficient risk of recurrence such that the harms of GnRHa injections are outweighed by the benefits of preventing resumption of ovarian function.

If GnRHa use is not planned following chemotherapy in women with chemotherapy-related amenorrhea (CRA), estradiol levels should be monitored closely for resumption of ovarian function if partnering with an AI.

2. What is the appropriate GnRHa timing and dose?

Appropriate GnRH agonists include goserelin, leuprolide, or triptorelin. At Dana-Farber, leuprolide is the preferred agent. Triptorelin is not available in the United States. Goserelin is not preferred due to the greater discomfort associated with injection due to the larger needle (14-16g) needed for injection of the subcutaneous implant. In contrast, leuprolide is injected as a reconstituted powder via a 21-23g needle.

What is the recommended dosing for leuprolide (Lupron®) monthly dose (3.75 vs 7.5 mg) and 3-month dose (11.25 vs 22.5 mg)?
Off label use for premenopausal women with breast cancer (UpToDate):

- Lupron Depot: IM; 3.75 mg q4 weeks
- Lupron Depot-3 month: IM; 11.25 mg q12 weeks

The higher dose (7.5 and 22.5mg) is also appropriate but should be reserved for instances in which the initial dose fails to suppress ovarian function or if preferred by the patient's insurance.

Adherence is essential. Therefore, it is important to reinforce that each dose should be given q4 weeks and not monthly, or q12 weeks and not every 3 months. In cases where following the precise schedule is not possible, early administration is preferred to late

administration. Insurance may not cover injections administered more than 2 days early and therefore it is recommended that authorization be confirmed for injections to be administered more than 2 days prior to the due date.

While most studies have used q4 week dosing of GnRH agonists, q12 week dosing appears to be similar in maintaining OFS. Among healthy patients, rates of OFS were similar with leuprolide 3.75 mg q4 week versus leuprolide 11.25 mg q12 week.[9] In a breast cancer patient population, the rate of breakthrough ovarian function (estradiol >30 pg/ml) with leuprolide 11.25 mg q12 week was <4%.[10] Similarly, in the GnRHa arm of the TABLE trial (which used leuprolide 11.25 mg q12 weeks), the rate of estradiol suppression at 1 and 2 years was >90%.[11] Another study showed essentially equivalent mean estradiol levels with q4 week goserelin versus q12 week leuprolide.[12] Additional studies have shown similar outcomes with q4 week vs q12 week goserelin).[13,14] An abstract presented at ASCO 2023 showed lower rates of breakthrough ovarian function with goserelin 10.8 mg q12 weeks vs goserelin 3.6 mg q4 weeks.[15] A recent retrospective matched cohort study of 950 patients treated with q4 week vs q12 week goserelin showed no difference in rates of breakthrough ovarian function, invasive disease-free survival, or overall survival with q4 week vs q12 week dosing.[6] In the Young Women's Breast Cancer Study, a large prospective cohort of women diagnosed with breast cancer at age ≤40, no difference was detected in breakthrough ovarian function with q4 week vs q12 week GnRHa dosing, using a validated ultrasensitive estradiol assay with a strict E2 cutoff of 2.72 pg/ml.[7] Similarly, no difference was detected in 12-month event-free survival with q4 week vs q12 week goserelin in another recent study using the ConcertAI Patient360 database.[16] In the ongoing NRG-BR009 (OFSET) trial, in which participants are randomized to optimal endocrine therapy including ovarian function suppression with versus without chemotherapy, GnRHa dosing frequency is at physician discretion.[17]

GnRHa are used routinely during chemotherapy as an adjunctive approach to fertility preservation and to reduce the risk of premature menopause. Studies that evaluated use of GnRHa in this setting used q4 week dosing, and treatment was initiated at least 1 week prior to start of chemotherapy.[18] We recommend q4 week dosing over q12 week dosing since this is the studied approach and, given the limited duration of chemotherapy, q4 week dosing does not add many injections relative to q12 week dosing, particularly since patients are frequently in clinic for chemotherapy. If q4 week dosing is not feasible, q12 week dosing can be substituted. While initiation of the GnRHa at least 1 week prior to chemotherapy is optimal, the GnRHa is often started simultaneously with chemotherapy, for instance for patients who are undergoing IVF just prior to chemotherapy or due to logistical reasons.

Recommendations

- For women age ≤40, we recommend q4 week dosing, particularly for those on an AI, but can offer the option of q12 week dosing for those who prefer it.
- We recommend the option of q4 week or q12 week dosing for women age >40.

Sequencing ovarian function suppression with endocrine therapy

Options include:

- Initiate the AI 4 weeks after initiation of the GnRHa.
- Initiate GnRHa and AI concurrently

We favor initiating the AI 4 weeks after the GnRHa to prevent the stimulation of ovarian estrogen production if the ovaries are not fully suppressed.

Based on the above-mentioned considerations, the BOC group came to the following consensus:

Consensus Statement

The recommended initial dosing for leuprolide (Lupron®) every 4 weeks (q4 weeks) is 3.75 mg and for q12 weeks is 11.25 mg.

For women age ≤40, we recommend q4 week GnRHa dosing, particularly for those on an AI, but can offer the option of q12 week dosing for those who prefer it. We recommend the option of q4 week or q12 week dosing for women age >40.

Higher dosing (Lupron 7.5 mg q4 weeks or 22.5 mg q12 weeks) is appropriate if preferred by insurance or insufficient OFS on the lower dose.

3. What is considered adequate suppression; when should we check estradiol +/- FSH; how long does it take to achieve ovarian suppression?

Vaginal bleeding/spotting occurring more than 4 weeks after starting a GnRHa should be assumed to represent breakthrough ovarian function. Pelvic cramping that resembles a period may also be an indication of breakthrough ovarian function as can substantial improvement in menopausal symptoms such as resolution of vaginal dryness without recent intervention. For patients with these symptoms, FSH and estradiol should be assessed. Various estradiol thresholds have been used to define breakthrough ovarian function in different studies. In the SOFT-EST substudy[5] of patients from SOFT on GnRHa plus AI, 3 cutoffs were evaluated:

- 2.72 pg/ml: Strictest cutoff for E2 thought to be inconsistent with use of an AI in postmenopausal women
- 10 pg/ml: Less strict cutoff for postmenopausal range on an AI
- 20 pg/ml: Inconsistent with GnRHa use

Rates of breakthrough ovarian function vary depending on the threshold applied. Young age and lack of prior chemotherapy are associated with a greater risk of experiencing breakthrough ovarian function.[5-7]

Limited data are available to inform whether breakthrough ovarian function impacts breast cancer outcomes among premenopausal women treated with GnRH agonists. A large, retrospective, matched cohort study found no difference in disease-free survival among patients with versus without breakthrough ovarian function, including using estradiol cutoffs of 30 pg/mL, 20 pg/mL, 10 pg/mL, and 5 pg/mL.[6] A recent analysis of the Young Women's Breast Cancer study, which used an ultrasensitive assay and an estradiol cutoff of 2.72 pg/ml, also showed no difference in invasive breast cancer-free survival among participants with versus without breakthrough ovarian function.[7] To our knowledge, no study to date has identified inferior outcomes among patients with breakthrough ovarian function. Nonetheless, it seems prudent to try to avoid prolonged breakthrough ovarian function for patients on an AI, given the theoretical concern that aromatase inhibitors could stimulate ovarian estrogen production if not fully suppressed.

The median E2 level for women on GnRHa plus tamoxifen is higher than that for women on GnRHa plus an AI, and the optimal cutoff likely differs between these regimens. Most commercial assays are less sensitive and have higher limits of detection, including a lower limit of detection of 10 pg/mL with the Mayo LC-MS assay available through Brigham and Women's Hospital. The Lin *et al.* study[6] evaluated different E2 cutoffs in an exploratory analysis, which revealed a trend towards inferior disease-free survival among patients with incomplete ovarian function suppression using the 5 pg/mL cutoff. However, the accuracy of the assay is lower at this level of detection.

Given the absence of data indicating inferior outcomes associated with breakthrough ovarian function and that tamoxifen is active even in the setting of ovarian estrogen production, we do not feel that monitoring estradiol levels is necessary for patients on OFS/tamoxifen based on currently available data. Given the concern that aromatase inhibitors are not effective in the setting of active ovarian function, we favor monitoring estradiol levels for premenopausal women on GnRHa plus an AI. We suggest monitoring estradiol levels 3 and 12 months after initiation, though it is reasonable not to monitor if preferred by the patient/provider, especially when ovarian function suppression is likely adequate based on clinical parameters including amenorrhea and other menopausal symptoms. When monitoring, estradiol should be drawn when the patient is due for the next GnRHa injection, rather than in the middle of the GnRHa cycle. While young age and absence of chemotherapy are independent risk factors for breakthrough ovarian function, the above monitoring strategy can be applied across all subgroups of premenopausal women treated with GnRHa plus an AI.

FSH levels have not been used to define breakthrough ovarian function and no specific cutoff has been proposed to determine the efficacy of GnRHa. It may be useful to check FSH at baseline and to obtain FSH levels in the setting of breakthrough ovarian function, in an effort to determine whether FSH is suppressed as it is a direct indicator of the pituitary's response to the GnRHa, and to consider other sources of high estrogen beyond residual

ovarian function including excess adipose tissue. However, FSH is not needed when routinely monitoring for breakthrough ovarian function.[19]

Ovarian function suppression generally occurs rapidly and within 4 weeks of GnRHa initiation.[6,20]

Based on the above-mentioned considerations, the BOC group came to the following consensus:

Consensus Statement

Ovarian suppression is usually accomplished within 4 weeks of first GnRHa injection. A postmenopausal estradiol level (<10 pg/ml using the Mayo liquid chromatography tandem mass spectrometry [LC-MS] assay) is consistent with ovarian suppression on both OFS/tamoxifen and OFS/AI and is considered adequate ovarian suppression. We suggest monitoring estradiol 3 and 12 months after initiation of OFS plus AI. Annual monitoring thereafter may be considered. FSH levels can be checked along with estradiol, and should be considered in situations where there is breakthrough ovarian function or when estradiol levels remain elevated despite modifications of GnRHa but a specific cutoff is not used to determine breakthrough ovarian function. We do not recommend monitoring estradiol levels for women on tamoxifen.

4. What should be done if breakthrough ovarian function occurs?

For patients with breakthrough ovarian function on GnRHa with concurrent use of an AI, we suggest considering switching from an AI to tamoxifen until ovarian suppression is obtained. Recognizing that some young women will be receiving adjuvant CDK4/6 inhibitors, which carry a higher risk of venous thromboembolism (VTE) when used with tamoxifen, the decision to switch should be individualized based on other VTE risk factors, such as obesity, smoking, and activity level.

For patients with breakthrough ovarian function on a GnRHa (including those on concurrent tamoxifen or an AI) with leuprolide 3.75 mg q4 weeks or 11.25 mg q12 weeks, we recommend increasing to 7.5 mg q4 weeks or 22.5 mg q12 weeks, respectively. Insurance may have a preferred or covered dose level and it is reasonable to appeal for use of a higher dose in the setting of breakthrough ovarian function. Of note, there are not data to support that breakthrough can be addressed with higher GnRHa dosing or that increasing dosing improves breast cancer outcomes.

Given that breakthrough ovarian function appears to be transient in most patients, for patients with low levels of breakthrough (estradiol 10-20 pg/mL), it is reasonable to continue current GnRHa dosing and repeat estradiol testing 4 weeks later.

Note that fulvestrant has modest cross reactivity (1-5%) in estradiol immunoassays, which can cause dramatically false-high estradiol results when sampling occurs in proximity to dosing. Estradiol measurement by mass spectroscopy has 1000-fold lower cross reactivity.

Consensus Statement

Breakthrough ovarian function, defined as vaginal bleeding or an estradiol level above the postmenopausal range, can be addressed by increasing the dose of the GnRHa and/or increasing the frequency of administration, though there are no available data supporting the efficacy of this practice, and limited available data do not demonstrate that breakthrough ovarian function on GnRHa is associated with worse breast cancer outcomes. Depending upon the clinical scenario and patient preferences, switching from an AI to tamoxifen until full ovarian suppression can be achieved should be considered. If there is a low degree of estradiol elevation (10-20 pg/ml) without symptoms of breakthrough ovarian function, it is reasonable to continue the current GnRHa dose and repeat an estradiol level 4 weeks later.

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