The Role of Ovarian Suppression in Premenopausal Women With Hormone Receptor-Positive Early-Stage Breast Cancer

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Here, we provide an in-depth review of the current evidence for the addition of ovarian suppression to adjuvant endocrine therapy, and we offer recommendations for clinical management.

Introduction

The optimal adjuvant endocrine therapy for premenopausal hormone receptor (estrogen receptor [ER], progesterone receptor [PR], or both)–positive breast cancer continues to evolve. Several meta-analyses have demonstrated that endocrine therapy in early-stage breast cancer confers a survival benefit and has a generally favorable toxicity profile.[1,2] At least 5 years of adjuvant tamoxifen has been the standard of care for premenopausal women for more than 2 decades and is recommended by the National Comprehensive Cancer Network (NCCN) Clinical Guidelines in Oncology and the 2014 American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines, based on level 1 evidence.[3,4] The value of adding ovarian suppression is unclear. In premenopausal women, cessation of ovarian function can be achieved on a temporary basis by pharmacologic interventions that inhibit ovarian production of estrogen, such as gonadotropin-releasing hormone (GnRH) agonists, or permanently by surgery (oophorectomy) or pelvic radiation (ovarian ablation). Given the inconclusive evidence supporting the use of ovarian suppression, ASCO has endorsed guidelines recommending that ovarian ablation or suppression not be added routinely to adjuvant therapy in premenopausal women.[5] International consensus guidelines have accepted the addition of GnRH agonists to tamoxifen or tamoxifen alone as standard endocrine therapies in premenopausal women, but they have admitted that evidence is lacking regarding the optimal duration of ovarian function suppression and note that this should be decided on an individual basis after discussion with the patient.[6] Here, we provide an in-depth review of the current evidence for the addition of ovarian suppression to adjuvant endocrine therapy, and we offer recommendations for clinical management.

Chemotherapy-Induced Amenorrhea Is Associated With Improved Survival

Several studies have demonstrated an improvement in survival in women who developed cessation of ovarian function after adjuvant chemotherapy (chemotherapy-induced amenorrhea) for early-stage breast cancer.[7,8] In the International Breast Cancer Study Group (IBCSG) 13-93 trial, 1,246 premenopausal women with axillary node–positive breast cancer were enrolled and received chemotherapy (cyclophosphamide plus either doxorubicin or epirubicin for 4 cycles, followed by immediate or delayed classical cyclophosphamide, methotrexate, and fluorouracil [CMF] for 3 cycles) followed either by tamoxifen for 5 years or no treatment.[7] Amenorrhea in this trial was defined as the absence of menses 15 months following randomization. Patients with ER-positive disease who achieved chemotherapy-induced amenorrhea had a significantly improved disease-free survival (DFS; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.44–0.86) compared with patients without amenorrhea, whether or not they received tamoxifen.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial investigated the impact of chemotherapy-induced amenorrhea on survival in 5,351 patients receiving sequential doxorubicin and cyclophosphamide (AC) followed by docetaxel (T); the doxorubicin-docetaxel combination (AT); or concurrent doxorubicin, cyclophosphamide, and docetaxel (TAC).[9] Among the 2,343 premenopausal patients with follow-up menstrual history who developed chemotherapy-induced amenorrhea (defined as no menstruation for at least 6 months during the 24-month follow-up), both overall survival (OS) and DFS were significantly increased (relative risk [RR], 0.76 and 0.70, respectively). In a 12-month landmark analysis, women with ER-positive tumors who had amenorrhea had a significantly better outcome than those who did not develop amenorrhea, with HR
for death of 0.52 (P = .002) and HR for disease recurrence, second malignancy, or death of 0.51 (P < .001).[10] Conversely, there was no significant difference in OS or DFS in women with ER-negative disease, regardless of amenorrhea status after chemotherapy. The antitumor effect of a lower estrogen state may offer a biologic basis for the plausibility of these results. Alternatively, chemotherapy-associated amenorrhea may simply represent a pharmacodynamic marker—of a particular patient’s pharmacogenomic variant that happens to affect individual toxicity and susceptibility to treatment.[11]

**Ovarian Suppression as a Single-Treatment Modality**

To evaluate the role of ovarian suppression as a single agent in the adjuvant setting, the 2005 Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) performed a meta-analysis of six trials that included nearly 8,000 women under the age of 50 with ER-positive or ER-unknown early-stage breast cancer, who were randomly assigned to ovarian suppression or no further treatment.[1] The age cut-off of 50 was used as a surrogate marker for menopausal status. Ovarian suppression significantly reduced breast cancer mortality (RR, 0.71) and risk of recurrence (RR, 0.75) at 15 years compared with observation but appeared to do so only in the absence of other systemic treatments. One limitation of this meta-analysis is that ER status was not tested in 63% of the patients who received ovarian ablation and in 26% of those who received ovarian suppression.

In contrast, the 2007 LHRH (luteinizing hormone–releasing hormone)-agonists in Early Breast Cancer Overview group meta-analysis examined 11,906 premenopausal patients with early-stage breast cancer randomized in 16 trials.[12] This analysis focused on the 9,022 patients with ER-positive breast cancer, and patients with ER-unknown status were not included. GnRH agonists were most commonly used for 2 years, although some trials had durations of 18 months, 3 years, or 5 years. When GnRH agonists were used as the only systemic adjuvant treatment (n = 407), there was no significant reduction in recurrence (P = .08) or death (P = .11) in patients with hormone receptor-positive cancers, although the number of patients in this comparison was small and the analysis was likely underpowered for these two outcomes.

While these data suggest that there might be a role for ovarian suppression as a single-treatment modality, it is not commonly used in patients with early-stage breast cancer and is not relevant to modern practice.

**Pharmacologic or Surgical Ovarian Suppression After Chemotherapy**

The 2005 EBCTCG meta-analysis, which reported significantly improved recurrence rate and survival in patients who received ovarian suppression (compared with those who received no adjuvant ovarian suppression), also assessed efficacy in trials where chemotherapy was equivalent in both arms:[1] There were no significant differences in the chemotherapy-only groups, except in women younger than 40 years, who achieved a significant reduction in recurrence with ovarian suppression (RR, 0.70; 95% CI, 0.39–0.96). The reliability of these findings in very young women is limited by the small number of patients in this subgroup analysis. The 2007 LHRH-agonists in Early Breast Cancer Overview group meta-analysis found that the addition of GnRH agonists to tamoxifen, chemotherapy, or both (n = 3,754) significantly reduced recurrence by 12.7% (95% CI, 2.4–21.9) and death by 15.1% (95% CI, 1.8–26.7).[12] Interestingly, GnRH agonists used alone demonstrated an efficacy similar to that of the chemotherapy regimens used in these trials, even though the majority of the chemotherapy regimens used were first-generation (66% of patients received a CMF-based regimen, and only 32% received an anthracycline-based regimen).

Individual studies suggest a benefit from ovarian suppression in patients treated with chemotherapy. In the North American Intergroup Trial (INT 0101, E5188), 1,503 premenopausal women with axillary lymph node-positive, ER-positive breast cancer were randomized to 6 cycles of cyclophosphamide, doxorubicin, and fluorouracil (CAF), CAF followed by 5 years of a GnRH agonist (monthly goserelin; CAF-Z), or CAF-Z with daily tamoxifen (CAF-ZT).[13] After a median follow-up of 9.6 years, there was a trend towards lower risk of mortality with CAF-Z compared with CAF (HR, 0.86; 95% CI, 0.68–1.08); however, with regard to the risk of recurrence, no benefit was seen (HR, 0.91; 95% CI, 0.74–1.11). Of note, there was no arm with tamoxifen only that could have been used to evaluate the impact of adjuvant chemotherapy followed by tamoxifen without ovarian function suppression.

A European multicenter trial evaluated 926 premenopausal women with either axillary node-positive or histologic grade 2 or 3 breast tumors randomized to adjuvant chemotherapy with or without ovarian suppression.[14] Ovarian suppression was achieved by radiation-induced ovarian ablation or triptorelin for 3 years. At a median follow-up of 9.5 years, there was no significant difference in OS...
(66% for chemotherapy alone vs 68% for chemotherapy plus ovarian suppression; \( P = .19 \)), except for women in the ovarian suppression arm who were under 40 years of age and who had ER-positive tumors; these women had a significantly decreased risk of recurrence (RR, 0.55; 95% CI, 0.34–0.88). In IBCSG Trial VIII, 1,063 pre- and perimenopausal women with axillary lymph node-negative breast cancer were randomized to receive goserelain alone for 24 months, 6 cycles of classical CMF chemotherapy alone, or 6 cycles of classical CMF followed by 18 months of goserelin.[15] In patients with ER-positive tumors, chemotherapy alone and goserelain alone resulted in similar 5-year DFS, whereas sequential therapy showed a trend for improved DFS compared with either modality alone. Since most of these studies evaluated ovarian suppression with a first-generation adjuvant chemotherapy regimen (ie, CMF), the relevance of the results in modern practice is limited.

**Ovarian Suppression in Combination With Tamoxifen**

Although chemotherapy-induced amenorrhea or ovarian suppression used as a single agent was associated with improved survival outcomes, the addition of ovarian suppression to tamoxifen does not confer a survival benefit in most women with ER-positive breast cancer. The 2007 EBGTCG analysis demonstrated no significant difference in either the risk of recurrence (HR, 0.85; 95% CI, 0.67–1.09) or the risk of death (HR, 0.84; 95% CI, 0.59–1.19) when a GnRH agonist was added to tamoxifen, compared with tamoxifen alone.[12] A phase III trial of the Eastern Cooperative Oncology Group (ECOG; E-3193, INT-0142), evaluated 345 premenopausal women with axillary node-negative, hormone receptor–positive breast cancers ≤ 3 cm who were randomized to tamoxifen alone vs tamoxifen plus ovarian function suppression.[16] In this study, adjuvant chemotherapy was not permitted. At a median follow-up of 9.9 years, there was no significant difference between the two arms with regard to DFS (5-year rate: 87.9% for tamoxifen vs 89.7% for tamoxifen plus ovarian suppression; \( P = .62 \)) or OS (5-year rate: 95.2% vs 97.6%; \( P = .67 \)). This study was terminated early because of slow accrual, and the sample size resulted in the trial being underpowered to reach a firm conclusion regarding survival. Nonetheless, the study population appeared to be low risk, and it is not surprising that the addition of ovarian suppression was not associated with improved outcomes.

In 2003, the IBCSG initiated two large international phase III trials, the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), to determine the value of adding ovarian suppression to tamoxifen or an aromatase inhibitor (AI), exemestane.[17,18] The primary analysis in SOFT included 2,033 premenopausal women randomized to either tamoxifen for 5 years or tamoxifen plus ovarian function suppression achieved by monthly triptorelin for 5 years, bilateral oophorectomy, or bilateral ovarian irradiation. Patients were stratified by receipt of chemotherapy. Patients who had received chemotherapy required a confirmatory premenopausal estradiol level within 8 months of completing chemotherapy, although adjuvant oral endocrine therapy was allowed before randomization.

At a median follow-up of 67 months, there was no significant difference in the primary endpoint of DFS between the patients receiving tamoxifen and those receiving tamoxifen plus ovarian suppression (5-year DFS, 84.7% vs 86.6%; HR, 0.83; 95% CI, 0.66–1.04; Table 1). However, after adjustment for covariates, tamoxifen plus ovarian suppression significantly reduced the risk of recurrence (HR, 0.78; 95% CI, 0.62–0.98). In particular, women who had not received prior chemotherapy did exceedingly well regardless of which arm they were assigned to; 98.6% of women in the tamoxifen arm and 98.7% of those in the tamoxifen-plus-ovarian-suppression arm were free from distant recurrence at 5 years. These patients were considered to have low-risk disease: 90.7% had node-negative disease, 84.9% had ≤ 2 tumors, 91.9% had grade 1 or 2 tumors, and 90.3% were aged 40 years or older.

Despite the lack of benefit in the overall population, exploratory analyses suggested that patients at higher risk for relapse might derive benefit from the addition of ovarian suppression to tamoxifen, including those treated with chemotherapy and very young women (under the age of 35 at the time of diagnosis of breast cancer). In those who were considered to have sufficient risk of recurrence to warrant chemotherapy and who remained premenopausal, the breast cancer–free interval (BCFI; freedom from invasive recurrence or contralateral breast cancer) at 5 years was 82.5% in the tamoxifen–ovarian suppression group and 78% in the tamoxifen-alone group (HR, 0.78; 95% CI, 0.6–1.02). In the secondary analysis comparing exemestane plus ovarian suppression to tamoxifen alone in patients who had received chemotherapy, the 5-year BCFI was further improved to 85.7% (HR, 0.65; 95% CI, 0.49–0.87). Similarly, most recurrences of breast cancer at distant sites occurred in patients who had received chemotherapy previously. In the chemotherapy cohort, the 5-year OS was significantly better in patients assigned to tamoxifen plus ovarian suppression than in those...
assigned to tamoxifen alone (95.5% vs 90.9%; HR, 0.64; 95% CI, 0.42–0.96), although these survival data are premature.

The most striking differences in outcomes were seen in the 350 women younger than 35 years of age. Of the women in this subgroup who were included in the primary analysis (n = 223), the 5-year BCFI was 67.7% for women assigned to tamoxifen, 78.9% for those assigned to tamoxifen plus ovarian suppression, and 83.4% for those assigned to exemestane plus ovarian suppression. Notably, 94% of this subgroup had received prior chemotherapy. In conclusion, this study demonstrated that adding ovarian suppression to tamoxifen did not improve DFS in the overall population, but that in certain high-risk cohorts of women, the addition of ovarian suppression might be associated with decreased risk of recurrence.

**Ovarian Suppression in Combination With Aromatase Inhibitors**

Emerging data support the use of ovarian function suppression in combination with AIs. AIs suppress plasma estrogen levels by inhibiting or inactivating aromatase, which is the enzyme responsible for the peripheral conversion of androgens to estrogens. The standard of care for adjuvant endocrine treatment in postmenopausal women includes AI therapy, based on randomized trials demonstrating a survival benefit for AIs compared with tamoxifen.[19] The efficacy of the various AIs (anastrazole, letrozole, and exemestane) is generally considered comparable.[19-21]

The Austrian Breast and Colorectal Cancer Study Group phase III trial (ABCSG-12) randomized 1,803 premenopausal women with ER-positive breast cancer to receive 3 years of ovarian suppression (goserelin) with tamoxifen or anastrazole, with or without the bisphosphonate zoledronic acid every 6 months.[22] Only 5.8% of patients had received chemotherapy. At a median follow-up of 7.9 years, there was no significant difference in DFS between patients who received ovarian suppression plus anastrazole and those who received ovarian suppression plus tamoxifen (HR, 1.13; 95% CI, 0.88–1.45), but there was a higher risk of death for anastrozole-treated patients (HR, 1.63; 95% CI, 1.05–1.45; Table 1)—findings contrary to those of SOFT. The investigators postulated that inferior survival might be due to acquired AI resistance, which could make post-relapse treatment more challenging.[23]

SOFT and TEXT also addressed the role of AI therapy in combination with ovarian suppression.[18] The SOFT and TEXT results were combined due to fewer events than expected, to allow for earlier reporting of the data. In the combined analysis, 4,690 patients were randomized to exemestane plus ovarian suppression or tamoxifen plus ovarian suppression; 57.4% had received chemotherapy. After a median follow-up of 68 months, the 5-year DFS was improved in the exemestane–ovarian suppression arm compared with the tamoxifen–ovarian suppression arm (91.1% vs 87.3%; HR, 0.72; 95% CI, 0.60–0.85). Patients in the exemestane–ovarian suppression arm had fewer distant recurrences at 5 years than those receiving tamoxifen plus ovarian suppression (93.8% vs 92.0%; HR, 0.78; 95% CI, 0.62–0.97). The difference was even greater in patients who had received prior chemotherapy. Of patients who did not receive chemotherapy and who were randomized to the exemestane-plus-ovarian-suppression group, over 97% remained free from breast cancer at 5 years. There was no significant difference in OS at 5 years between the two groups (95.9% in patients receiving exemestane–ovarian suppression and 96.9% in those receiving tamoxifen–ovarian suppression), although longer follow-up is required. In conclusion, these data indicate improved outcomes for premenopausal women receiving exemestane plus ovarian suppression.

**Toxicities Associated With Ovarian Suppression**

The addition of ovarian suppression to hormone therapy increased the frequency of toxicities seen in these patients (Table 2). In the patients in the North American Intergroup Trial (E-3193, INT-0142) who received ovarian suppression, grade 3 or higher toxicities were more common—in particular, there were more menopausal symptoms, lower sexual activity, and lower health-related quality of life.[16]

Of patients enrolled in SOFT, 16.7% of those in the tamoxifen-plus-ovarian-suppression group discontinued their treatment early compared with 21.7% of those in the tamoxifen-only group, suggesting that the addition of ovarian suppression does not lead to increased discontinuation rates.[17] At 4 years of therapy, 21.9% of patients were not adherent to ovarian suppression, and at 67 months, only 25.8% were continuing some or all of their hormone therapies. Grade 3 or 4 targeted adverse events were more frequently seen in the tamoxifen-plus-ovarian-suppression arm than in the tamoxifen-alone arm (31.3% vs 23.7%). The addition of ovarian suppression led to more frequently reported hot flushes and sweating; decreased libido; and more musculoskeletal
complaints, glucose intolerance, osteoporosis, and hypertension. Patient-reported outcomes were obtained from 1,722 women in SOFT who were assigned to either tamoxifen or tamoxifen plus ovarian function suppression.[24] Patients completed questionnaires every 6 months for the first 24 months and then annually between years 3 and 6. Patients who received ovarian suppression were significantly more affected by hot flushes, sleep problems, and loss of sexual interest, although these all improved over time. These symptoms were less pronounced in patients who had received prior chemotherapy. Vaginal dryness was more frequent in the ovarian suppression group and was sustained over the whole treatment period, whereas more vaginal discharge was seen in those receiving tamoxifen alone. Despite these differences in endocrine and sexual symptoms, changes in global quality of life (mood and physical well-being) were similar between the two arms.

About 14% of patients in TEXT stopped protocol-assigned treatments early, with more patients in the exemestane-plus-ovarian-suppression arm doing so than in the tamoxifen-plus-ovarian-suppression arm (16% vs 11%).[18] Targeted adverse events of grade 3 or 4 were similar between the exemestane arm (30.6%) and the tamoxifen arm (29.4%). Fractures, musculoskeletal symptoms, vaginal dryness, and decreased libido were reported more frequently in the exemestane arm, whereas thromboembolic events, hot flushes, and urinary incontinence were more frequent in the tamoxifen arm. Osteoporosis was more common in the exemestane arm than in the tamoxifen arm (13.2 vs 6.4%). Depression was reported in 50.3% of patients in the exemestane arm and in 50.1% of those in the tamoxifen arm, with 4.1% overall reporting grade 3/4 depression. Changes in quality-of-life indicators and coping were similar between the two groups. The investigators felt that the adverse event profile seen in TEXT was similar to that seen in postmenopausal women generally. Given these data, it is important to consider side effects, their impact on quality of life, and adherence when choosing between tamoxifen, tamoxifen plus ovarian suppression, and an AI plus ovarian suppression.

**Expert Opinion**

In light of the recent data from the SOFT and TEXT combined analysis and the ABCSG-12 trial, it is clear that ovarian suppression does not improve outcomes in the overall population of premenopausal women with ER-positive early-stage breast cancer, and particularly in women thought to have low-risk disease (eg, low-grade disease, small tumors, no receipt of chemotherapy). However, there does appear to be a role for ovarian suppression in certain subsets. In a preplanned analysis, the SOFT and TEXT data showed us that women who were considered by their providers to harbor sufficient risk of recurrence and who had received chemotherapy derived a benefit in 5-year DFS from the addition of ovarian suppression to either tamoxifen or exemestane. Likewise, patients who were under the age of 35 derived significant benefit from the addition of ovarian suppression, although it is notable that the vast majority of these patients had received chemotherapy and generally had higher-risk disease. TEXT showed us that women had a significant improvement in 5-year DFS if ovarian suppression was combined with an AI as opposed to tamoxifen, although the absolute improvement was small (a 4-percentage point increase in 5-year DFS with exemestane plus ovarian suppression compared with tamoxifen plus ovarian suppression). Conversely, ABCSG-12 did not demonstrate any differences in DFS between the anastrazole and tamoxifen arms, in both of which patients were treated with ovarian function suppression. Moreover, the 5-year OS in patients receiving anastrazole plus ovarian suppression was inferior to the rate in those receiving tamoxifen plus ovarian suppression, whereas the SOFT and TEXT trials showed no difference in OS. Possible reasons for this discordance in results may be the smaller number of patients enrolled in the ABCSG-12 study and the fact that the endocrine therapies were given for a total of 3 years, instead of 5 years as in TEXT. Three years of AI therapy may not have been sufficient—unlike 3 years of tamoxifen, which is known to have a carryover protective effect on breast cancer recurrence. Finally, women in ABCSG-12 who received the bisphosphonate zoledronic acid had a significantly better DFS compared with those who did not receive zoledronic acid; only a minority of patients in SOFT and TEXT received bisphosphonates. The role of bisphosphonates as a component of adjuvant treatment for early-stage breast cancer remains controversial.

Although very young women and those who had received chemotherapy appeared to benefit from the addition of ovarian suppression in SOFT/TEXT, this benefit was associated with additional toxicities. Women who received an AI plus ovarian suppression noted more musculoskeletal complaints, greater loss of sexual interest, and more vaginal dryness, whereas women who received tamoxifen plus ovarian suppression reported more hot flushes and sweats. The tolerability of therapy...
(eg, toxicity) in an individual patient can have a major impact on adherence to treatment, which may ultimately influence treatment efficacy and outcomes.[25] When balancing efficacy and adverse event profiles, it may be prudent to save ovarian suppression for only those most likely to benefit—higher-risk women. How one defines “high risk” is debatable but would likely include patients with higher-stage disease, lymph node-positive disease, higher histologic grade, and very young age, among other factors.

The recently reported ovarian suppression studies were well conducted and included an enormous number of women recruited on an international platform, although some limitations exist. We do not have long-term follow-up on these studies, and therefore the OS benefit cannot be truly evaluated. It is questionable whether one would subject a young woman to the toxicities of ovarian suppression if it did not translate to an improvement in OS. Likewise, the use of DFS as the primary endpoint is probably not appropriate when evaluating early-stage disease. Also, these studies do not address the question of the optimal duration of therapy, although when they were designed, the results of the Adjuvant Tamoxifen—To Offer More (aTTom) trial and the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which support the use of 10 years of tamoxifen based on a survival benefit, were unknown.[26,27] In light of the aTTom and ATLAS data, it is questionable whether ovarian suppression with an endocrine agent should be continued past 5 years. The potential long-term consequences and impact on quality of life are not fully characterized at the current time. SOFT and TEXT demonstrated increases in diabetes, heart disease, and osteoporosis, but it is not clear whether these increases will translate to more deaths from these conditions, particularly in very young women. Finally, we do not know how the results of SOFT/TEXT can be integrated into our modern era of genomic testing. It might be of interest to analyze the differences between the effects of ovarian suppression, tamoxifen, and exemestane as these correlate with genomic findings. Much like the way in which we use genomic assays such as the Oncotype DX Recurrence Score to help decide which patients might derive a benefit from chemotherapy, perhaps a similar assay could be used to decipher which endocrine agent(s) should be recommended to our patients.

**Conclusion**

Progress has been made in our understanding of the role of adjuvant ovarian function suppression in premenopausal women with early-stage breast cancer, but many questions remain. Numerous prior studies have convincingly shown a clear benefit from adjuvant endocrine therapy. For women with low-risk disease, the addition of ovarian suppression to either tamoxifen or an AI does not add a substantial benefit. In the higher-risk subset, ovarian suppression should be considered and discussed with patients. The additional toxicities of ovarian suppression must be kept in mind when deciding whom to treat.

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Table 1: Efficacy Data in Select Phase III Trials of Ovarian Suppression...

Table 2: Select Adverse Events Increased In Patients Receiving Ovarian...

**References:**


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