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Investigating Ovarian Function in Pre-Menopausal Estrogen Receptor-Positive Breast Cancer: A Cross-Sectional Study

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Abstract

Background: Ovarian function suppression (OFS) plays a vital role in the treatment of premenopausal hormone-positive breast cancer patients. Still, some patients experience incomplete ovarian function suppression. Therefore, we aimed to investigate the prevalence of incomplete OFS in premenopausal hormone-positive breast cancer patients and identify associated risk factors.

Method: This cross-sectional study was conducted at Javad Al-Aeme Clinic from January to February 2024.We enrolled premenopausal hormone-positive breast cancer patients aged 18 to 55 who had been treated with a Gonadotropin-releasing hormone agonist (GnRH agonist) combined with an aromatase inhibitor for at least three months. The relationship between incomplete OFS and variables including age, body mass index (BMI), treatment duration, and type of GnRH agonist was analyzed. All statistical analyses were performed using Stata version 17.

Results: A total number of 47 patients, with a mean age of 43.36 years (standard deviation (SD: 5.55) and a mean BMI of 26.88 kg/m² (SD:4.22) participated in this study. Among these patients, 23 (49%) had estradiol levels greater than 20 pg/ml, indicating incomplete OFS. Although no significant relationship was found between the variables and ovarian escape, the odds for ovarian escape were higher in younger patients and those with a higher BMI. Patients treated with goserelin at doses of 3.6 mg and 10.8 mg exhibited similar odds of ovarian escape, both of which were higher than those observed in patients treated with triptorelin 3.75 mg.

Conclusion: The high prevalence of incomplete OFS highlights the importance of monitoring ovarian function in high-risk pre-menopausal hormone-positive breast cancer patients.

Keywords: Breast neoplasm, Aromatase inhibitor, Gonadotropin-releasing hormone agonist, Premenopausal

Introduction

Endocrine therapy for postmenopausal estrogen receptor-positive breast cancer patients typically includes tamoxifen or aromatase inhibitors (AIs). Previous studies have demonstrated that AIs have a 30% lower recurrence rate than tamoxifen in postmenopausal patients,[1] making them the preferred treatment option. In contrast, premenopausal patients exhibit positive feedback on the pituitary gland and increased estrogen levels.[2]

The primary source of estrogen production in premenopausal women is the ovaries. However, in premenopausal patients, the serum estradiol level should be comparable with that in postmenopausal patients. Therefore, suppressing ovarian function can decrease estradiol production. Ovarian function can be suppressed through methods such as oophorectomy, radiotherapy, or the use of Gonadotropin-releasing hormone agonist (GnRH agonists). Previous studies have shown that the efficacy of these methods is comparable.[3]

GnRH agonists work by stimulating the luteinizing hormone–releasing hormone (LHRH) receptor in the pituitary gland, which downregulates sensitivity to LHRH and reduces the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This reduction ultimately leads to decreased estradiol production and secretion by the ovaries Additionally, in premenopausal patients, various tissues, including fat, can convert androgens to estrogen through the action of the aromatase enzyme. Inhibiting the aromatase enzyme helps to reduce estrogen production.[4]

Significant studies, such as the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), indicate that combining ovarian function suppression (OFS) with AIs increases disease-free survival and overall survival in premenopausal estrogen receptor-positive breast cancer patients.[5]

In the SOFT-EST study, which assessed levels of estradiol (E2), estrone (E1), and estrone sulfate (E1S) over one year, it was found that 34% of patients had a serum estradiol level greater than 2.72 pg/mL. Additionally, 25%, 24%, and 17% of patients had estradiol serum levels exceeding this threshold at 3, 6, and 12 months, respectively.[6] Another study by Burn et al. showed that 24% of patients had serum estradiol levels exceeding 20 pg/mL, a phenomenon referred to as "ovarian escape".[7]

Incomplete OFS has been demonstrated in various studies,[8-11] with differing prevalence rates and associated risk factors. Thus, premenopausal patients with active ovarian function and those receiving AIs may have higher serum estradiol levels than postmenopausal patients at every time point of endocrine therapy and ovarian function suppression.[7] Estrogen promotes tumor progression and recurrence by binding to its receptors.[12] Therefore, assessing ovarian function in premenopausal patients is critical. The present study aimed to determine the prevalence of incomplete OFS in premenopausal hormone-positive breast cancer patients and to identify the associated risk factors.

Method

Study design

We conducted a cross-sectional study at Javad Al-Aeme Clinic in Kerman from January to February 2024. The study focused on premenopausal hormone receptor-positive breast cancer patients who met specific eligibility criteria for participation. The primary objective was to evaluate the prevalence of incomplete OFS and to identify associated risk factors. Patients included in this study had different durations from the time of starting endocrine therapy to the time that was included in the study; thus, patients were divided into three groups (Group one: patients who were on OFS plus AI from 3-6 months; Group two: patients who were on OFS plus AI for 6-12 months; Group three: patients who were on OFS plus AI for more than 12 months). This study received approval from the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (Ethics approval code: IR.KMU.AH.REC.1402.171). All participants provided informed consent prior to enrollment in the study.

Table 1. Characteristics of premenopausal hormone-positive breast cancer patients based on ovarian function status

Characteristics	Ovarian suppression	Ovarian escape	Total
Number	24 patients	23 patients	47 patients
Age	43.96 (5.10)	42.74 (6.04)	43.37 (5.55)
BMI	26.52 (4.91)	27.21 (3.55)	26.88 (4.22)
Duration of treatment			
3 to 6 months	6 (12.70%)	1 (2.20%)	7 (14.80%)
6 to 12 months	11 (23.60%)	15 (32.00%)	26 (55.60%)
12 months and more	7 (14.80%)	7 (14.80%)	14 (14.80%)
Type of GnRH agonist			
Triptorelin 3.75 mg	4 (8.52%)	5 (10.64%)	9 (19.16%)
Goserelin 3.6 mg	9 (19.15%)	9 (19.15%)	18 (38.30%)
Goserelin 10.8 mg	10 (21.27%)	10 (21.27%)	20 (42.54%)

Ovarian escape> 20 pg/dl, ovarian suppression≤20 pg/dl, BMI: Body mass index

Variables

In previous studies, various factors have been examined, including age, body mass index (BMI), prior chemotherapy, serum levels of FSH and LH, type of AI, duration of treatment with a GnRH agonist, and tumor characteristics. In our study, however, certain variables were consistent across participants: all had a prior history of chemotherapy, and all were treated with 25 mg of exemestane.

Age, BMI, duration of endocrine therapy, and type of GnRH agonist are considered factor variables. In contrast, estradiol, FSH, and LH serum levels are dependent variables. Age and BMI are categorized as confounding variables.

Data source

Demographic information—including age, sex, and immunohistochemical data for tumors post-surgery—along with details of the endocrine and chemotherapy regimens, was extracted from patients' files at Javad Al-Aeme clinic.

Estradiol level

Estradiol levels serve as a predictor of OFS but do not have a definitive threshold. Previous studies, including SOFT-EST[6] and the Hormonal Bone Effect (HOBOE),[14] by Burn et al.[7] and Lin et al., identified varying thresholds for estradiol: 2.72, 10-40, 20, and 30 pg/mL for premenopausal patients with breast cancer, respectively.[6-11, 13, 14] In our study, estradiol serum levels were measured using a chemiluminescent microparticle immunoassay (CMIA) (Siemens, Munich, Germany). We established a threshold of 20 pg/mL for identifying ovarian escape. Patients with estradiol levels above 20 pg/mL were classified as experiencing ovarian escape, indicating incomplete ovarian function suppression.

LH and FSH

Serum levels of LH and FSH were also assessed using the CMIA method (Siemens, Munich, Germany), which has a lower detection limit of 0.01 pg/mL.

Bias

To mitigate selection and measurement biases, we included all eligible participants in the study and employed standardized, automated protocols for hormone assays. Additionally, confounding variables were managed using multivariable analysis techniques.

Statistical analysis

In this study, the dependent variables included serum estradiol, LH, and FSH levels. In contrast, the independent variables comprised age, BMI, duration of treatment, and type of GnRH agonist. Age and BMI were found to exhibit a normal distribution, for which descriptive statistics, including the mean and standard deviation, were used. In contrast, serum estradiol, FSH, and LH showed a skewed distribution; therefore, central statistics such as medians and interquartile ranges were used to describe the variables of the study (Table 1).

To investigate the effects of different variables on ovarian escape, a logistic regression analysis was conducted to examine the relationship between age and BMI. Fisher's exact test was employed for treatment duration and type of GnRH agonist. The relationship of each variable with ovarian escape was assessed based on effect size, *P*-value, and 95% confidence interval (CI).

The odds ratios were reported as crude values, and adjusted for age, BMI, treatment duration, and type of GnRH agonist (Table 2). All analyses were conducted using STATA version 17 (StataCorp, 2021). Statistical significance was defined as two-tailed $P < 0.05$ for all tests.

Results

Between January 2024 and February 2024, 47 premenopausal women with breast cancer participated in this study. Among the 47 patients, 23 (49%) had an estradiol serum level above 20 pg/dL, and 24 (51%) had an estradiol serum level like that of postmenopausal patients.

The mean age of the patients was 43.36 (5.54) years (Figure 1). In this study, age was not related to the incidence of ovarian escape (odds ratio (OR): 0.96, CI: 0.86 to 1.06, $P = 0.45$), but the mean age of the patients with ovarian escape was 1.2 years younger than that of patients with ovarian suppression (Table 2).

The mean BMI value was 26.88 (4.2) (Figure 1). BMI and incomplete ovarian suppression were not related to each other (OR: 1.05, 95% CI: 0.91 to 1.021, *P*-value: 0.49), but patients with ovarian escape had a BMI of 0.7 kg/m^2 greater than that of patients with ovarian suppression (Table 2).

The study participants had different durations of OFS plus an AI, and patients were categorized into three groups: Group one: started endocrine therapy 3 to 6 months before the study was conducted; Group two and Group three: started ovarian suppression 6 to 12 months before the survey was conducted (OR: 8.19, 95% CI: 0.70 to 94.82, *P* value: 0.04) and 12 months or more before the study started (OR: 6.00, 95% CI: 0.45 to 79.22, *P* value: 0.12), respectively. The frequency durations of the patients are summarized in table 1.

Patients in this study were treated with three different GnRH agonists (triptorelin 3.75 mg, goserelin 3.6 mg, and goserelin 10.8 mg); the GnRH agonist data of the patients are summarized in table 1. No correlation was found between duration of endocrine treatment ($P = 0.136$) and type of GnRH ($P = 1$).

The median LH serum level in patients was 1.02 (0.01–1.1) pg/mL, and the median LH concentrations in ovarian escape and ovarian suppression patients were 0.39 (0.02–0.36) and 1.64 (0.02–0.36), respectively. The median FSH serum level in patients was 12.02 (4.9–18.94) pg/mL, and the median FSH concentrations in ovarian escape and ovarian suppression patients were 10.78 (5.5–15.31) and 13.23 (5.79–17.52) pg/mL, respectively.

Discussion

In this single institution cross-sectional study, 47 breast cancer patients participated, and

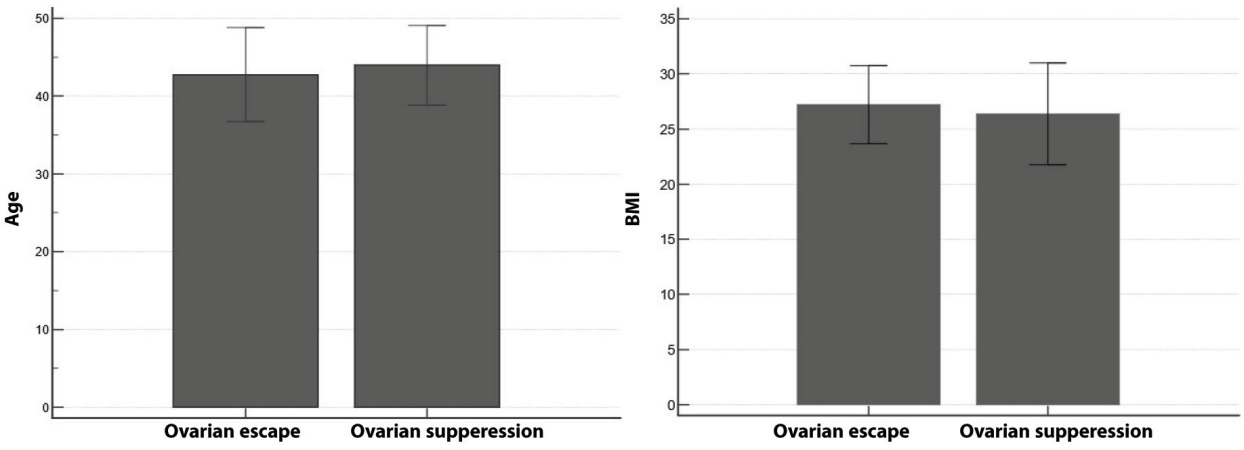

Figure 1. This figure shows the mean age and BMI in the ovarian escape and ovarian suppression groups. Patients in incomplete ovarian suppression group were younger than patients who had complete ovarian suppression. Patients who had incomplete ovarian suppression had higher BMI than patients who had achieved complete ovarian suppression.
BMI: Body mass index

approximately 50% exhibited estradiol levels exceeding 20 pg/ml, categorizing them as having incomplete ovarian function suppression, or 'ovarian escape'.[1]

Similar studies have shown a different prevalence of ovarian escape from 5 to 50%.[6-12, 13-15] Similar to a study by Lin et al. on 950 breast cancer patients, half of whom were treated with ovarian function suppression with monthly injections, 5.5% of patients with OFS with monthly injections had at least one serum estradiol level above the established limit.[10] In the SOFT-EST study,[6] 34.2% of patients had at least one estradiol level greater than 2.72 pg/ml.[6] Similarly, in a study conducted by Burn et al.[7] on 46 breast cancer patients, 23.9% of patients had estradiol levels greater than 20 pg/mL three months after the start of ovarian suppression.

Our investigation found a notably higher incidence of incomplete ovarian suppression, which may be attributable to our estradiol measurement methodology, specifically the use of chemiluminescent immunoassays. While this technique is widely accessible across various healthcare settings, it is inherently less precise compared with methodologies such as gas chromatography. Moreover, another contributing factor to the increased prevalence may be metabolites generated by AIs, which could cross-react with our detection method.[16]

Recent theories have emerged regarding incomplete ovarian suppression, with one positing that antibody production against the polypeptide structures of goserelin and leuprolide plays a significant role. These antibodies have the potential to bind to the GnRH agonists, effectively hindering their actions.[17,18]

Our study did not demonstrate a significant correlation between age and ovarian suppression. Interestingly, the patients experiencing incomplete ovarian suppression had a median age that was 1.2 years younger than those who achieved complete ovarian function suppression. However, in a study conducted on 46 breast cancer patients by Burn et al.,[7] younger patients had a significantly higher chance of ovarian escape. Also, in a study by Liu et al.[10] involving 435 breast cancer patients under the age of 49, patients younger than 35 years had an increased likelihood of experiencing incomplete OFS compared with their counterparts aged between 35 and 40 years.

Table 2. Univariate and multivariate analyses for variables associated with incomplete ovarian function suppression in premenopausal hormone-positive breast cancer patients

Variable(s)	OR	95% CI
Age crude	0.959	0.86 to 1.06
BMI crude	1.051	0.91to 1.21
Age adjusted	0.946	0.84 to 1.06
BMI adjusted	1.076	0.91 to 1.26

OR: Odds ratio, CI: Confidence interval

Also, in a study by Chen et al.,[8] the only variable that affected ovarian escape was age. On the other hand, in other studies, including SOFT-EST[6] and Tesch et al.,[15] age was not significantly related to ovarian escape. Younger patients, due to their better ovarian reserve, have a greater chance of recovering ovarian function and returning estradiol levels to higher levels than postmenopausal patients. Therefore, in these patients, ovarian function suppression should be more cautious and monitored regularly to avoid causing ovarian escape and treatment failure.

We observed that while patients with elevated estradiol levels had a higher BMI, no significant association was found between increased BMI and the incidence of incomplete ovarian function suppression. The SOFT-EST study[6] demonstrated a significant correlation between higher BMI and an increased likelihood of estradiol levels surpassing 2.72 pg/ml. Additionally, similar findings were reported in other studies indicating that individuals with higher BMI are more prone to incomplete ovarian function suppression.[9]

Obese patients typically have a higher proportion of adipose tissue, which produces estradiol via aromatization of testosterone and dehydroandrostenedione by the aromatase enzyme. Consequently, patients with elevated BMI exhibit increased estradiol levels compared with those with lower BMI.

Patients included in this study had different durations from the start of ovarian function suppression to the time of inclusion in the study; the duration of endocrine therapy and ovarian escape were not significantly related. However,

the odds of ovarian escape in patients on OFS plus AI for 6 to 12 months were 8 times greater than those in patients on OFS and AI for 3 to 6 months; patients on OFS plus AI had 6 times greater odds of ovarian escape than patients on OFS for 3 to 6 months, and the odds of ovarian escape in patients treated for 6 to 12 months were 33% greater than those in patients who were on OFS plus AI for more than 12 months. Our results revealed that patients undergoing treatment for less than one year had a greater likelihood of experiencing incomplete ovarian suppression in comparison with those treated for over a year. Previous studies suggested that patients exhibiting incomplete OFS in the initial months tend to achieve adequate estradiol levels by 12 months of treatment.[10,15] The findings of SOFT-EST indicated that the incidence of estradiol levels exceeding 2.72 pg/ml was 25%, 24%, and 17% at 3, 6, and 12 months, respectively,[6] during OFS coupled with AIs. This reflects a decreasing trend in the likelihood of incomplete OFS over time. Also, Fleege et al. observed that the prevalence of ovarian escape decreased by 17.5% one year after the start of ovarian function suppression compared with 35 days after starting OFS.[9]

LH and FSH are secreted from the pituitary gland and stimulate ovaries to produce and release estrogen and progesterone. First, GnRH agonist injections increase FSH and LH serum levels, but in subsequent injections, FSH and LH levels are downregulated by the GnRH agonist. In this study, the median serum levels of LH and FSH were higher in patients undergoing ovarian suppression than in those with ovarian escape. Consequently, in patients undergoing ovarian suppression, a lower estradiol concentration exerts positive feedback on the pituitary gland, resulting in increased serum levels of FSH and LH. In both SOFT-EST[6] and HOBOE[14] studies, LH was greater, and FSH was lower in patients with OFS plus an AI than in patients with OFS plus tamoxifen.[19] Additionally, previous research has shown that FSH levels can recover after prolonged treatment, facilitating ovarian stimulation and subsequently leading to estradiol production, thereby resulting in incomplete ovarian suppression.[13]

To our knowledge, there has been no comprehensive study assessing breast cancer in the Iranian context, highlighting an urgent need for further research to determine the extent and confirm the elevated likelihood of incomplete ovarian suppression among Iranian patients.

One of the main limitations of the present study was the small sample size due to being a single-institution study. Another limitation was the lack of a plan for following up the patients over time and comparing their estradiol serum levels 3 or 6 months later. Yet, this cross-sectional study can be continued as a cohort study in future. Another limitation of the study was the assessment of ovarian function only with estradiol.

Conclusion

We aimed to assess OFS in premenopausal hormone-positive breast cancer patients. In this study, 49% of the patients did not have serum estradiol levels below 20 pg/dl after three months of treatment with OFS plus an AI. None of the variables had a significant relationship with ovarian escape, but previous studies have demonstrated that younger and obese patients, and patients with prior history of chemotherapy have an increased chance of ovarian escape. Breast cancer patients whose serum estradiol levels are not the same as those of postmenopausal patients should be monitored.

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Authors' Contribution

N.N: Study design and reviewing the manuscript; A.KP: Study design, data gathering, drafting, and reviewing the manuscript; A.N: Data gathering, drafting; F.N: Data analysis, drfting; All authors have read and approved the final

manuscript and agreed to be accountable for all aspects of the work.

Conflict of Interest

None declared.

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