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Comparison of suboptimal versus adequate ovarian function suppression in premenopausal women with early breast cancer treated with adjuvant endocrine therapy: An exploratory analysis of two prospective studies

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ABSTRACT

Purpose: Ovarian function suppression (OFS) combined with tamoxifen or aromatase inhibitor (AI) are standard treatment options for young women with hormone receptor-positive breast cancer. Suboptimal OFS may reduce the efficacy of the endocrine treatment (ET). This study evaluated factors associated with suboptimal OFS induced by gonadotropin-releasing hormone agonist (GnRHa).

Methods: PREFER (NCT02895165) and GIM 23-POSTER (NCT05730647) are multicentric Italian prospective, observational studies enrolling premenopausal women undergoing (neo)adjuvant chemotherapy and/or ET. The present analysis includes only patients enrolled at the coordinating center. Patients receiving ET with OFS were classified into suboptimal (estradiol >25.1 ng/L measured by chemiluminescent immunoassay or resumed menstruation) or adequate OFS.

Results: As of June 2024, 488 patients were enrolled (median follow-up: 44.4 months, IQR 20.6–84.0). Of 343 patients receiving adjuvant ET, 315 were in the adequately suppressed group and 28 in the suboptimal suppression group (of whom 55.9 % and 92.9 %, respectively, were receiving an AI). Clinical characteristics (age, BMI, baseline FSH, and estradiol levels) and previous chemotherapy (with or without concurrent GnRHa) showed no association with suboptimal OFS. Concurrent treatment with AI was the only factor significantly associated with suboptimal OFS (HR 12.83, 95 % CI 3.01–54.65; p = 0.001). The proportion of patients with suboptimal suppression was 5.1 % (95 % CI 3.2–8.2) in the first year of ET, rising to 10.5 % (95 % CI 7.1–15.4) within five years.

Conclusions: Approximately 10 % of premenopausal women receiving GnRHa as part of adjuvant ET did not achieve complete OFS. Use of AI was the only factor linked to suboptimal OFS.

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1. Background

Approximately 70 % of breast cancers express hormone receptors [1]. Adjuvant endocrine treatment (ET) represents a cornerstone for patients with hormone receptor-positive (HR+) disease [2–5]. For premenopausal women with high-risk HR+ early breast cancer, it is recommended to combine an aromatase inhibitor (AI) with ovarian function suppression (OFS), commonly achieved using a gonadotropin-releasing hormone agonist (GnRHa). A patient-level meta-analysis of 15,000 women from 25 randomized trials examining the addition of OFS (vs not) in premenopausal women showed an improvement in the 15-year risk of BC recurrence of 12.1 % and mortality of 8.0 % [6]. Additionally, a recent trial-level network meta-analysis showed consistent benefit of adding OFS to ET in all premenopausal populations, even with a lower risk of recurrence [7].

The administration of a GnRHa to achieve OFS is not always effective. The SOFT-EST sub-study evaluated the level of estradiol (E2), estrone (E1), and estrone sulfate (E1S) during the first year of adjuvant ET in patients with early breast cancer receiving triptorelin plus exemestane or tamoxifen [8]. Considering E2 levels up to 2.72 pg/mL as indicating adequate suppression, at 12 months 34 % of patients receiving triptorelin plus exemestane had at least one E2 level over 2.72 pg/mL, and 17 % had all E2 over the threshold at each time point (every 3 months). This is a crucial aspect since AI could not only have a stimulating effect on ovarian function and E2 production, but the hormonal elevation could have a detrimental effect on breast cancer outcomes [9–12]. International guidelines do not recommend a specific schedule for assessing E2 levels during OFS treatment, leaving the timing of evaluation to the discretion of physicians [2,13].

A recent survey drew attention to the variations in current guideline recommendations on the optimal E2 measurements and the optimal management of suboptimal OFS, underlining the variations in clinical practice [14].

Given the uncertainties on this crucial topic, we conducted an exploratory analysis to investigate the rate and the main related features of suboptimal OFS during GnRHa treatment within two Italian prospective, observational studies (PREFER and GIM 23-POSTER) enrolling premenopausal women eligible for adjuvant ET.

2. Materials and methods

2.1. Study design

PREFER and GIM 23-POSTER study designs were previously reported [4,15–17].

Briefly, PREFER (NCT02895165) is an ongoing, prospective cohort study conducted across 23 Italian institutions affiliated with the Gruppo Italiano Mammella (GIM) group, evaluating oncofertility care in young women with breast cancer. The PREFER study includes premenopausal patients (18–45 years) who were candidates for (neo)adjuvant chemotherapy and not previously exposed to anticancer therapies.

GIM 23-POSTER (NCT05730647) is an ongoing, multicenter, prospective, observational study aiming to evaluate ET choices in premenopausal patients diagnosed with HR+ early breast cancer.

In the PREFER study, follicle-stimulating hormone (FSH), E2, and anti-mullerian hormone serum levels are assessed at baseline, during chemotherapy, at the end of chemotherapy, and annually thereafter. In GIM 23-POSTER, hormonal assessments are performed according to the practice of treating physicians.

All patients provided a written informed consent before study entry. The studies were approved by the Ethics Committee of the coordinating center.

2.2. Study population and hormonal evaluation

For the present analysis, we included all patients from PREFER and GIM 23-POSTER enrolled at the coordinating center (IRCCS Ospedale Policlinico San Martino, Genoa, Italy), treated with GnRHa and with at least one hormonal assessment reported (E2 and FSH) during the follow-up (at least 3 months after the start of ET). The analysis was restricted to the coordinating center to ensure homogeneity and completeness of hormonal data, as all E2 and FSH assays were performed in a single certified laboratory using the same CLIA method and standard operating procedures. This approach minimized variability in assay performance across sites and guaranteed consistent data quality. We excluded patients who had hormone receptor-negative disease, those with no or unknown use of GnRHa, or with missing information on ET. All patients were treated according to clinical practice and received triptorelin 3.75 mg intramuscularly/subcutaneously or leuprorelin 3.75 mg intramuscularly every 28 days. The concurrent ET treatment could be tamoxifen or AI. The definition of suboptimal OFS (E2 > 25.1 ng/L) was based on the analytical characteristics of the CLIA assay used at our institution, which has a lower sensitivity (15ng/L) compared with liquid chromatography-tandem mass spectrometry methods employed in other studies. Hormonal samples were collected according to clinical practice, typically at follow-up visits, without standardized timing across patients. In patients who received chemotherapy, GnRHa was initiated either concurrently with chemotherapy or immediately after its completion, and hormonal assessments used for this analysis were performed at least three months after the start of endocrine therapy plus GnRHa, thereby reflecting ovarian function during established ovarian suppression rather than early post-chemotherapy recovery.

Based on E2 levels or resumption of menstruation at least 3 months after the start of ET plus GnRHa, patients were divided into two groups: patients with suboptimal OFS (suboptimal suppression group) and patients with adequate OFS (suppressed group).

As per study inclusion criteria, all patients enrolled in PREFER received prior chemotherapy.

2.3. Study objective

The primary objective of this analysis was to evaluate the proportion of women with HR+ early breast cancer who experienced suboptimal OFS through the evaluation of the E2 levels during adjuvant ET.

Secondary objectives included the evaluation of the factors (i.e., type of GnRHa administered, use of previous chemotherapy, BMI, age, basal E2 level) associated with suboptimal E2 suppression.

2.4. Statistical methods

Categorical variables were summarized as percentages, while continuous variables were summarized as medians and IQR. The cumulative incidence of suboptimal OFS was plotted to illustrate the proportion of patients without optimal OFS over time. Adjustment in the final model was made for variables associated with suboptimal OFS in univariate analysis ($p < 0.20$). The final adjustment was made for the use of chemotherapy, the type of GnRHa, and AI use. Chemotherapy exposure was categorized as no chemotherapy, anthracycline- or taxane-based chemotherapy, or combined anthracycline plus taxane-based chemotherapy. Chemotherapy was also included as a binary variable (yes vs no) in the multivariable model to adjust for potential confounding. All statistical analyses were two-sided, with P values< 0.05 considered statistically significant. The analyses were performed using Stata, software version 16.1 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Patients' characteristics

Out of 1863 patients with early breast cancer registered in PREFER and GIM 23-POSTER between 2011 and 2023, 488 were enrolled in the coordinating center (363 in PREFER and 126 in GIM 23-POSTER).

Among them, 104 patients were excluded because they had HR-negative breast cancer, 22 because they did not receive GnRHa, 11 because they did not receive adjuvant ET, and 8 because of missing follow-up information, resulting in 343 patients included in the final analysis (Figure 1).

Among the included patients, 315 (91.8 %) had adequate OFS during follow-up (adequate OFS group), while 28 (8.2 %) did not (suboptimal OFS group). Among the 28 patients with suboptimal OFS, 2 (7.1 %) experienced menstrual resumption, whereas 26 (92.9 %) had only biochemical evidence of incomplete suppression (estradiol >25.1 ng/L). The median age at diagnosis was 39 years (interquartile range [IQR] 36–43), and BMI was 22.1 kg/m^2 (IQR 20.0–24.7). A total of 258 patients (75.2 %) received chemotherapy, of whom 231 (89.5 %) started GnRHa concurrently with chemotherapy. The companion ET was AI in 202 (58.9 %) patients, and tamoxifen in 141 (41.1 %). Baseline characteristics according to suppression status are reported in Table 1. Baseline hormonal and clinical data were not available for all patients: FSH and estradiol values were missing in 22 % and 19 % of cases, respectively; information on smoking status was available for 68 % of patients, and *BRCA* mutation status for 61 %. The proportion of missing values was similar across the adequately suppressed and suboptimal suppression groups.

3.2. Ovarian suppression outcome

In univariate analysis, use of AI was associated with a higher risk of suboptimal OFS (HR 12.83; 95 % CI 3.01–54.65; p = 0.001), while use of chemotherapy, alone or in combination with a GnRHa, and the type of GnRHa were not associated with suboptimal OFS (Table 2).

In univariate analysis, chemotherapy category was not significantly associated with suboptimal ovarian suppression (p = 0.345). In the multivariable model, chemotherapy exposure (yes vs no) was also not significantly associated with OFS failure (HR 0.55, 95 % CI 0.24–1.29; p = 0.170). In the multivariate analysis, use of AI was the only covariate that remained significantly associated (HR 12.19; 95 % CI 2.81–52.99; p = 0.001) (Table 3).

Median follow-up was 44.4 months (IQR, 20.6–84.0) overall, 42.0 months for patients with adequate OFS (IQR, 20.1–85.1) and 60.5 months for patients with suboptimal OFS (IQR, 33.1–81.4).

The percentage of patients with suboptimal OFS increased over time, with 5.1 % at one year (95 % CI, 3.2–8.2), 6.2 % at two years (95 % CI, 4.0–9.6), 7.2 % at three years (95 % CI, 4.7–11.0), 8.4 % at four years (95 % CI, 5.6–12.5), and 10.5 % at five years (95 % CI, 7.1–15.4) (Figure 2).

Among patients treated with AI the percentages were higher as compared with the overall population: 8.2 % at one year (95 % CI, 5.0–13.3), 10.1 % at two years (95 % CI, 6.5–15.7), 12.1 % at three years (95 % CI, 7.9–18.3), 14.4 % at four years (95 % CI, 9.5–21.5), and 19.3 % at five years (95 % CI, 12.8–28.6) (Figure 3).

Following the detection of suboptimal OFS, management was adapted according to clinical practice: two patients underwent surgical oophorectomy based; two had adjustment of GnRHa administration schedule from every 28 days to every 21 days; and in the remaining patients, the ET was switched from an AI to tamoxifen, while continuing GnRHa

Although oncologic outcomes were not a predefined endpoint of this analysis, descriptive data were collected to provide a clinical context. After a median follow-up of 44.4 months, 30 patients (8.8 %) experienced disease recurrence and 4 (1.2 %) died, yielding an estimated 5-year DFS rate of approximately 89.4 % (95 % CI, 84.0–93.0). Due to the small number of events, no formal comparison between the adequate and suboptimal OFS groups was performed.

4. Discussion

Our findings suggest that nearly 10 % of premenopausal women treated with adjuvant AI or tamoxifen plus GnRHa did not achieve an adequate OFS throughout 5 years of treatment, and that the AI use was the only factor significantly associated with an increased risk of suboptimal ovarian suppression.

Although OFS is a standard component of adjuvant therapy for premenopausal women with HR+ early breast cancer at intermediate or

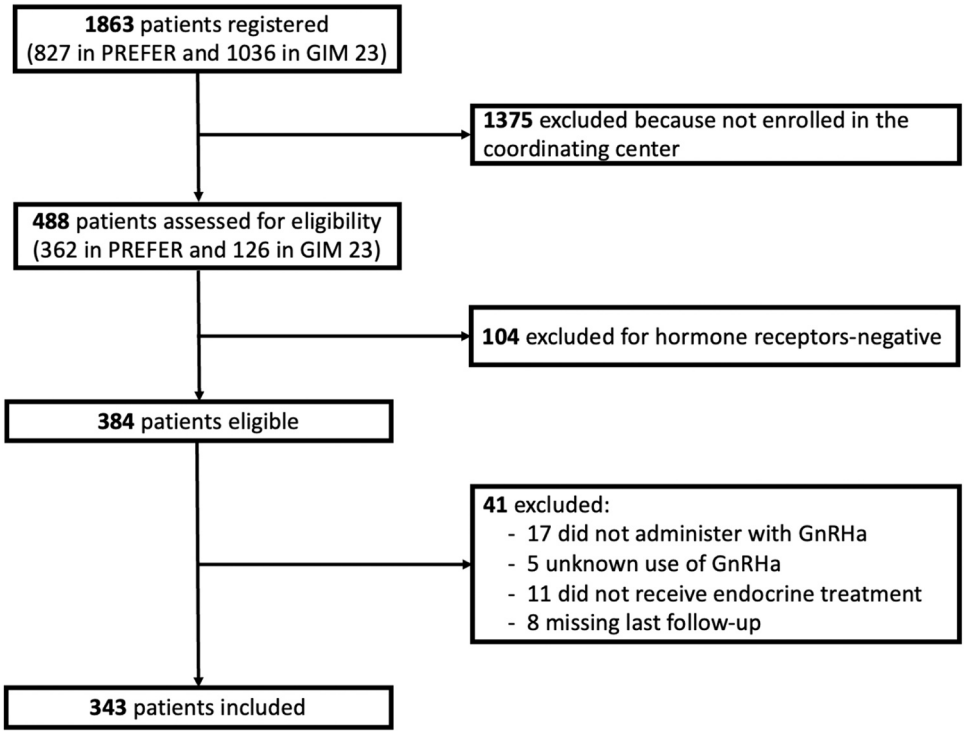

Fig. 1. Participant flow. Legend: GnRHa, gonadotropin-releasing hormone agonist.

Table 1
Baseline characteristics according to ovarian suppression.

	Adequate ovarian suppressionN (%) n = 315	Suboptimal ovarian suppressionN (%) n = 28	TotalN (%) n = 343
Age at diagnosis, median (IQR) years	39 (36–43)	38 (33–44)	39 (36–43)
BMI, median (IQR) yearsMissing	22.2 (19.9–24.8)1	21.6 (20.7–22.9)0	22.1 (20.0–24.7) 1
Basal FSH, median (IQR) yearsMissing	6.0 (3.8–8.5) 170	5.9 (5.2–7.9)14	6.0 (3.9–8.6) 184
Basal estradiol, median (IQR) yearsMissing	77 (37–131) 168	63 (39–113)14	75 (38–125) 182
Smoking habit			
No	102 (32.4)	18 (64.3)	120 (35.0)
Yes (Current+Ex)	48 (15.2)	5 (17.9)	53 (15.5)
Missing	165 (52.4)	5 (17.9)	170 (49.6)
BRCA mutation			
No	118 (37.5)	22 (78.6)	140 (40.8)
Yes	15 (4.8)	1 (3.6)	16 (4.7)
Missing	182 (57.8)	5 (17.9)	187 (54.5)
Histology			
Ductal	278 (88.2)	24 (85.7)	302 (88.1)
Lobular	25 (7.9)	2 (7.1)	27 (7.9)
Other	11 (3.5)	2 (7.1)	13 (3.8)
Missing	1 (0.3)	0 (0.0)	1 (0.3)
Previous pregnancy			
No	97 (30.8)	10 (35.7)	107 (31.2)
Yes	197 (62.5)	18 (64.3)	215 (62.7)
Missing	21 (6.7)	0 (0.0)	21 (6.1)
Chemotherapy			
No	77 (24.4)	8 (28.6)	85 (24.8)
Anthracycline or taxane	17 (5.4)	1 (3.6)	18 (5.3)
Both	221 (70.2)	19 (67.9)	240 (70.0)
GnRHa during chemotherapy*			
No	25 (10.5)	2 (10.0)	27 (10.5)
Yes	213 (89.5)	18 (90.0)	231 (89.5)
Type of GnRHa			
Leuprorelin	180 (57.1)	19 (67.9)	199 (58.0)
Triptorelil	135 (42.9)	9 (32.1)	144 (42.0)
Aromatase inhibitors			
No	139 (44.1)	2 (7.1)	141 (41.1)
Yes	176 (55.9)	26 (92.9)	202 (58.9)
Breast surgery			
Conservative	164 (52.1)	16 (57.1)	180 (52.5)
Mastectomy	151 (47.9)	12 (42.9)	163 (47.5)
Axillary surgery			
Sentinel	196 (62.2)	17 (60.7)	213 (62.1)
DLA	110 (34.9)	10 (35.7)	120 (35.0)
Missing	9 (2.9)	1 (3.6)	10 (2.9)
Anti-HER2 therapy			
No	232 (73.7)	17 (60.7)	249 (72.6)
Yes	83 (26.3)	11 (39.3)	94 (27.4)
Type of anti-HER2 therapy**			
Trastuzumab	64 (77.1)	9 (81.8)	73 (77.7)
Pertuzumab+Trastuzumab	15 (18.1)	1 (9.1)	16 (17.0)
Other	4 (4.8)	1 (9.1)	5 (5.3)
Radiotherapy			
No	85 (27.0)	9 (32.1)	94 (27.4)
Yes	230 (73.0)	19 (67.9)	249 (72.6)
Tumor size			
T1	145 (46.0)	13 (46.4)	158 (46.1)
T2	116 (36.8)	11 (39.3)	127 (37.0)
T3-T4	34 (10.8)	2 (7.1)	36 (10.5)
Missing	20 (6.3)	2 (7.1)	22 (6.4)
Nodal status			
N0	139 (44.1)	13 (46.4)	152 (44.3)
N1	127 (40.3)	12 (42.9)	139 (40.5)
N2-N3	26 (8.2)	2 (7.1)	28 (8.2)
Missing	23 (7.3)	1 (3.6)	24 (7.0)
Tumor grading			
G1	18 (5.7)	1 (3.6)	19 (5.5)
G2	206 (65.4)	19 (67.9)	225 (65.6)
G3	72 (22.9)	7 (25.0)	79 (23.0)
Missing	19 (6.0)	1 (3.6)	20 (5.8)
HER2 status			
Negative	234 (74.3)	18 (64.3)	252 (73.5)
Positive	81 (25.7)	10 (35.7)	91 (26.5)

*only for CT=Yes
** only for Anti-HER2 therapy=Yes
Legend: N, number; IQR, interquartile range; BMI, body mass index; FSH, follicle stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist.

Table 2
Univariate analysis of suboptimal ovarian suppression according to baseline characteristics.

	HR	*95 % CI*	*P-value*
Age at diagnosis	0.98	0.92–1.05	0.615
BMI	0.96	0.87–1.07	0.455
Basal FSH	1.01	0.99–1.04	0.382
Basal estradiol	1.00	0.99–1.01	0.818
Smoking habit			0.452
No	Ref.	-	
Yes (Current+Ex)	0.68	0.25–1.85	
BRCA mutation			0.300
No	Ref.	-	
Yes	0.35	0.05–2.57	
Previous pregnancy			0.810
No	Ref.	-	
Yes	0.91	0.42–1.97	
Chemotherapy			0.345
No	Ref.	-	
Anthracycline or taxane	0.45	0.06–3.58	
Both	0.55	0.24–1.28	
Chemotherapy			0.154
No	Ref.	-	
Yes	0.54	0.24–1.26	
GnRHa during chemotherapy			0.346
No chemotherapy	1.86	0.80–4.35	
No GnRH during chemotherapy	1.14	0.26–4.91	
Yes GnRH during chemotherapy	Ref.	-	
Type of GnRHa			0.078
Leuprorelin	Ref.	-	
Triptorelin	0.48	0.22–1.08	
Aromatase inhibitors			**0.001**
No	**Ref.**	**-**	
Yes	**12.83**	**3.01–54.65**	
Anti-HER2 therapy			0.227
No	Ref.	-	
Yes	1.60	0.75–3.41	

Legend: HR, hazard-ratio; CI, confidence interval; BMI, body mass index; FSH, follicle stimulating hormone; Ref., reference; GnRHa, gonadotropin-releasing hormone agonist.

high risk of recurrence, detailed recommendations for its practical implementation and monitoring remain limited [2].

Recently, the American Society of Clinical Oncology (ASCO) conducted a survey to better understand current practice patterns and variations in GnRHa treatment. This survey reported significant differences in several aspects of GnRHa use in clinical practice: 92 % of those surveyed would like guidance on all aspects of OFS, indicating substantial uncertainty about the optimal E2 measurements and premenopausal status definition according to hormone-level thresholds, as well as management of suboptimal OFS or timing [14].

In our study, we found that the use of AI as an endocrine agent in association with GnRHa was associated with an increased risk of suboptimal suppression during the treatment period. Indeed, even if after

Table 3
Multivariate analysis of suboptimal ovarian suppression according to baseline characteristics.

	HR	*95 % CI*	*P-value*
Chemotherapy			0.170
No	Ref.	-	
Yes	0.55	0.24–1.29	
Type of GnRHa			0.657
Leuprorelin/Enantone	Ref.	-	
Triptorelin/Decapeptyl	0.83	0.37–1.88	
Aromatase inhibitors			**0.001**
No	**Ref.**	**-**	
Yes	**12.19**	**2.81–52.99**	

Legend: HR, hazard-ratio; CI, confidence interval; Ref., reference; GnRHa, gonadotropin-releasing hormone agonist

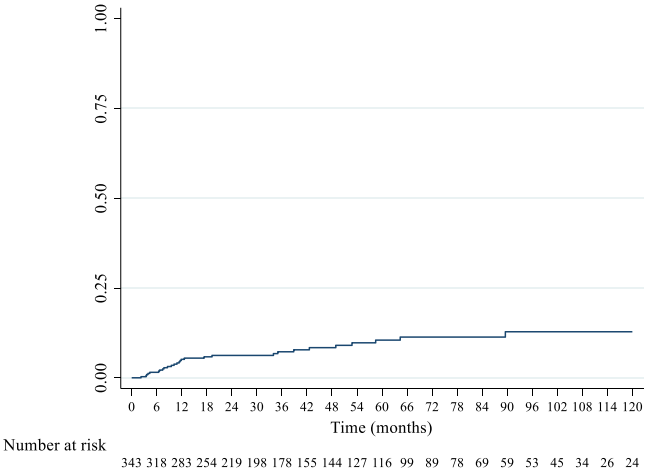

Fig. 2. Cumulative suboptimal ovarian suppression in the overall population.

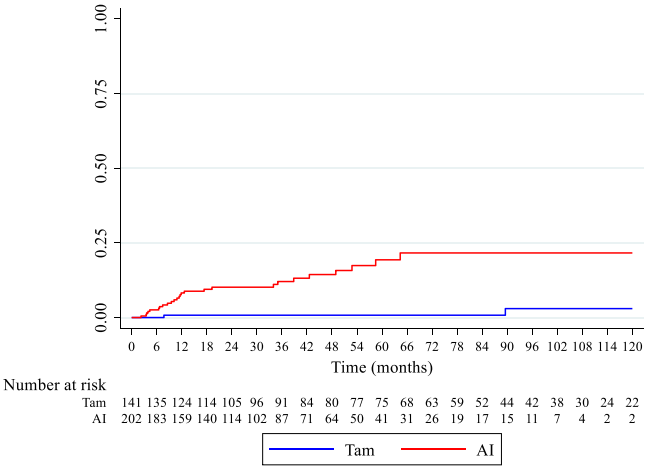

Fig. 3. Cumulative suboptimal ovarian suppression in patients treated with aromatase inhibitors plus GnRHa or Tamoxifen plus GnRHa. Legend: Tam, tamoxifen; AI, aromatase inhibitors.

the first year of treatment 8.2 % of patients display suboptimal OFS, after five years of treatment this percentage grows up to 19.3 %. In this analysis, suboptimal ovarian function suppression was defined based on the detection of a single E2 value above the predefined threshold or the resumption of menses during treatment with GnRHa. Importantly, within routine clinical practice, any biochemical or clinical evidence of inadequate OFS prompted immediate intervention, such as modification of the GnRHa agent or dosing schedule. Consequently, sustained or recurrent biochemical escape was not observed, as persistent elevations were actively prevented by timely management.

The biological mechanism underlying AI-associated suboptimal OFS likely involves disinhibition of the hypothalamic-pituitary-gonadal axis. AIs reduce the peripheral aromatization of androgens to estrogens, thereby reducing negative feedback on GnRH secretion and leading to a compensatory increase in gonadotropins (FSH and LH) [18–20]. This hormonal rebound may reactivate residual ovarian function despite ongoing GnRHa treatment, resulting in incomplete suppression of E2 levels [21]. Ensuring effective ovarian suppression is therefore critical when combining AIs with GnRHa to avoid potential estrogen escape and compromised therapeutic efficacy [2,5].

Recovery of ovarian function has been linked to worse DFS, distant relapse-free survival, and OS [22]. A matched case-control study conducted by Ingle et al reported that, in breast cancer patients treated with adjuvant AI, an estradiol level $\geq$ 0.5 pg/mL after six months of treatment is related to a 2.2-fold increased risk of an early breast cancer event compared to patients with E2 level $<$ 0.5 pg/mL ($p = 0.0005$) [12]. However, the optimal method and threshold for assessing ovarian suppression remain unclear. According to the European Society of Endocrinology, the definition of menopause is a clinical diagnosis based upon cessation of menses for at least 12 months; however, for chemotherapy-induced menopause, ovarian function may resume after 12 months of amenorrhea, depending on the age of the woman and the dose and duration of treatment [23]. In premenopausal patients receiving ET plus GnRHa, the administration of GnRHa modifies the endocrine axis, with an expected decrease in both FSH and estradiol levels, without a univocal cut-off. Consistent with our findings, the SOFT-EST sub-study reported variable rates of suboptimal OFS depending on assay sensitivity and timing of hormone testing [8]. The authors found that 34 % of patients had an E2 level $>$ 2.72 pg/mL at least at one measurement. Similarly to our results, no baseline clinical characteristics were significantly associated with a higher risk of suboptimal OFS.

Other prospective and randomized studies have similarly shown that hormonal recovery during adjuvant endocrine therapy remains frequent, regardless of baseline clinical characteristics or type of GnRHa used [24–26].

When suboptimal OFS is detected, several strategies may be considered. These include switching to a different GnRHa formulation or modifying administration intervals (e.g., triptorelin 3.75 mg every 3 weeks rather than every 4 weeks) [14]. For selected high-risk patients or those with recurrent ovarian reactivation, definitive ovarian ablation (either surgically or via radiotherapy) remains an alternative [27–29]. Further research is warranted to define standardized management algorithms for suboptimal OFS and to evaluate their impact on oncologic outcomes.

From a clinical standpoint, our findings underscore the importance of monitoring E2 levels in premenopausal women receiving AI plus OFS. Although current guidelines do not mandate routine hormonal testing, evidence from the SOFT-EST and other prospective studies supports periodic E2 assessment to ensure adequate suppression [2,13]. Implementing standardized hormonal monitoring could help detect suboptimal OFS early and allow timely management, such as adjusting GnRHa dosing schedules, switching formulations, or, in selected cases, considering definitive ovarian ablation. Establishing consensus recommendations on monitoring frequency and management strategies will be essential to translate these findings into clinical practice.

Our study has several limitations that warrant highlighting. The definition of suboptimal OFS relied on an E2 threshold of $>$ 25.1 ng/L (approximately 6.9 pg/mL), corresponding to the detection limit of the CLIA assay used at our center. This differs from LC–MS/MS-based studies, such as SOFT-EST, where a stricter threshold ($>$2.72 pg/mL) was adopted. Given the higher detection limit of CLIA, our approach may have underestimated the true prevalence of incomplete ovarian

suppression. However, using the same assay across all samples ensured internal consistency and avoided inter-laboratory variability; however, future implementation of LC-MS/MS may improve detection of true ovarian escape, especially in patients treated with AI plus OFS. Despite the prospective enrollment and the same assay used to assess estradiol level, estradiol and FSH measurements were not collected at standardized time points nor systematically synchronized with GnRHa injections, which may have contributed to variability in measured estradiol levels and potential misclassification of OFS status. This limitation reflects routine clinical practice and should be considered when interpreting the results. It should be noted that hormonal measurements in our analysis were obtained after establishment of GnRHa-induced ovarian suppression; therefore, the observed estradiol elevations more likely reflect late ovarian escape during ongoing OFS rather than early recovery from chemotherapy-induced amenorrhea. In addition, baseline data for FSH, estradiol, smoking status, and *BRCA* mutation were missing for a considerable proportion of patients, reflecting the real-world nature of these prospective registries. This incomplete information may have limited the statistical power to identify additional predictors of suboptimal OFS. Nevertheless, missing data were balanced between comparison groups, reducing the likelihood of systematic bias. Although both PREFER and GIM 23-POSTER are multicenter studies, in the present analysis, we included only data from the coordinating center, thus reducing the heterogeneity in the management of patients. While this choice limited external validity and may introduce selection bias, it allowed for uniform hormone measurements and consistent data collection. Notably, baseline clinical and treatment characteristics of patients from the coordinating center are comparable to those of the broader PREFER and GIM 23-POSTER cohorts, as reported in their primary publications. Lastly, while our exploratory data on oncologic outcomes suggest a low event rate consistent with the short follow-up, longer observation will be essential to determine whether suboptimal OFS translates into differences in DFS or OS.

In conclusion, about 10 % of premenopausal women receiving GnRHa as part of adjuvant ET did not achieve complete OFS, particularly those treated with AIs. These findings emphasize the importance of assessing OFS in patients on AI plus GnRHa and call for prospective studies with longer follow-up to optimize management of suboptimal suppression and clarify its prognostic implications.

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Declaration of Competing Interest

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