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REVIEW

Ovarian Escape in Hormone Receptor-Positive Breast Cancer: Mechanisms, Risk Factors, Clinical Consequences, and Management Strategies

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Abstract: Ovarian function suppression (OFS) is essential in the treatment of premenopausal patients with hormone receptor-positive breast cancer. However, during therapy with gonadotropin-releasing hormone analogs (GnRHa), some patients may experience a phenomenon known as "ovarian escape" in which levels of gonadotropins and estradiol return to premenopausal ranges, indicating partial or complete recovery of ovarian function. This phenomenon may markedly compromise the efficacy of endocrine therapy and increase the risk of breast cancer recurrence and disease progression. At present, there is no universally accepted or standardized definition for "ovarian escape" nor are there recognized diagnostic criteria. In clinical research, a serum estradiol threshold of 2.72 pg/mL is frequently employed as a reference standard for effective OFS. Systematic reviews have shown that different studies report varying incidence rates, diagnostic methods, and interpretations regarding its clinical significance, further adding to the complexity of this issue. Therefore, this review aims to systematically analyze key topics related to "ovarian escape" including its underlying mechanisms, potential risk factors, clinical consequences, and feasible management strategies, with the goal of providing scientific evidence and guidance for clinical practice.

Keywords: breast cancer, ovarian function suppression, ovarian escape

Introduction

Breast cancer is now the most prevalent malignancy among women worldwide, according to the International Agency for Research on Cancer (IARC) of the World Health Organization.[1] In China, onset tends to occur at a younger age, with peak incidence between 45 and 49 years; approximately 60% of cases are diagnosed before menopause, and these patients often exhibit higher recurrence rates and poorer prognoses.[2,3] Hormone receptor–positive (HR+) tumors account for 70–80% of breast cancers, and their growth is strongly driven by estrogen.[4] In premenopausal women, suppression of ovarian function to lower estrogen levels can effectively reduce the risk of tumor proliferation and metastasis. Randomized clinical trials, including SOFT and TEXT, have demonstrated that combining OFS with endocrine therapy improves outcomes. In particular, the addition of OFS to tamoxifen or aromatase inhibitors significantly reduces recurrence and prolongs disease-free survival compared with tamoxifen alone, with the greatest benefit observed in high-risk subgroups such as lymph node–positive patients or those who have received chemotherapy.[5–8]

OFS can be achieved through pharmacological agents, radiotherapy, or surgical oophorectomy. Pharmacological suppression with gonadotropin-releasing hormone analogues (GnRHa) is generally preferred due to its reversibility.[9] However, some patients experience "ovarian escape" during GnRHa or other OFS regimens, in which ovarian function recovers despite treatment. This is marked by rising gonadotropin and estradiol levels to premenopausal ranges, often accompanied by the return of menses. Patient-related variables such as younger age and higher body mass index (BMI) have been recognized as important risk factors for incomplete ovarian suppression, with younger women exhibiting greater ovarian reserve and higher baseline estradiol levels, and obesity facilitating peripheral estrogen production through increased aromatase activity. Ovarian

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escape undermines therapeutic efficacy and may adversely affect disease control. Consequently, close monitoring of endocrine parameters is essential, enabling timely adjustment of treatment strategies. Here, we examine the mechanisms, risk factors, diagnostic approaches, and management options for ovarian escape, with the aim of informing clinical practice.

Mechanisms of Ovarian Escape: Why Does Suppression Fail?

Ovarian escape is a multifactorial phenomenon arising from pharmacological, physiological, and individual patient variables. Ovarian suppression agents act primarily through modulation of the hypothalamic–pituitary–ovarian axis to inhibit steroid hormone production. The most widely used agents are GnRH agonists and antagonists. GnRH agonists (GnRHa), such as leuprolide and goserelin, are structurally analogous to endogenous GnRH and bind pituitary GnRH receptors. Treatment begins with a transient stimulatory phase—the "flare effect"—during which receptor activation increases follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, temporarily elevating estrogen levels.[10] With continued administration, sustained receptor occupancy induces downregulation and desensitization of GnRH receptors, rendering the pituitary refractory to stimulation and markedly reducing FSH and LH secretion.[10–12] As follicular development and estradiol synthesis depend on gonadotropin stimulation, this reduction to postmenopausal levels effectively suppresses ovarian steroidogenesis, producing a reversible drug-induced menopausal state.[12]

GnRH antagonists (GnRH-ant), such as elagolix and degarelix, bind pituitary GnRH receptors with high affinity but without intrinsic activity, thereby blocking endogenous GnRH signaling.[13–15] Unlike agonists, antagonists act immediately, avoiding the flare effect and inducing a rapid decline in LH and FSH within days.[16] The resulting loss of stimulation to granulosa and theca cells sharply reduces estradiol concentrations.

The mechanisms underlying ovarian escape remain incompletely understood. Some studies suggest that certain patients may develop antibodies against GnRHa, which structurally resemble GnRHa and interfere with the drug's receptor binding, thereby reducing its efficacy.[17–19] In these patients, antibody titers increase with each administration and significantly decrease upon discontinuation.[19] Regarding drug metabolism, GnRHa, as a nonapeptide, offers advantages such as resistance to endopeptidase degradation and multiple administration routes. However, individual differences in drug metabolism may contribute to reduced responsiveness to GnRHa in certain patients. Prolonged use of GnRHa can lead to downregulation of pituitary GnRH receptors, rendering target cells insensitive and reducing FSH and LH levels to postmenopausal levels. However, insufficient dosage or inappropriate administration intervals may result in receptor recycling and functional recovery in the pituitary, thereby inducing ovarian escape.

Additionally, ovarian escape may be associated with unexplained insufficient suppression of FSH. By continuously stimulating the pituitary, GnRHa inhibits LH and FSH secretion, thereby reducing estrogen synthesis. However, this suppression is not entirely effective. Some studies have observed that FSH levels return to baseline after treatment in certain patients. Early systematic reviews of GnRHa monotherapy reported this phenomenon, showing that although LH suppression persisted, FSH levels gradually recovered one month after treatment.[20,21] Similarly, similar findings were observed in breast cancer patients treated with goserelin or leuprolide acetate.[22] Researchers hypothesize that this recovery is due to incomplete suppression of the negative feedback mechanism. In endocrine-related studies of goserelin with or without tamoxifen (TAM), it was found that adding TAM prevented FSH level recovery and significantly reduced plasma estradiol concentrations in the combination group.[23] This result suggests that FSH recovery may be a critical factor contributing to estradiol elevation.[24] Furthermore, the lack of effect of GnRHa on the α-gonadotropin subunit or FSH-β subunit genes may also be implicated in this phenomenon, leading to insufficient regulation of pituitary function.[25] When GnRHa is used alone, although LH remains continuously suppressed without significant rebound, FSH gradually returns to baseline after several months, which is believed to be associated with inhibitory proteins in the negative feedback mechanism.[22] The FSH rebound during this process further promotes estradiol secretion, thereby triggering ovarian escape.

GnRHa may alter the expression of locally produced gonadotropic substances such as activin and follistatin in the pituitary through direct or indirect pathways.[22] Meanwhile, some autocrine and paracrine signaling factors are also believed to independently regulate gonadotropic substance expression or alter pituitary responsiveness to GnRH. For instance, studies have demonstrated that abnormal expression of pituitary adenylate cyclase-activating polypeptide (PACAP), prolactin (PRL), and prostaglandins (PG) can affect GnRH release and its downstream effects, leading to asynchronous secretion of LH and

FSH.[25,26] These complex mechanisms collectively may be key contributors to the occurrence of "escape" phenomena in certain patients during GnRHa treatment.

Risk Factors for Ovarian Escape: Which Patients Should Be Vigilant?

The risk factors for incomplete OFS are not yet fully understood, but existing studies suggest that its occurrence may be associated with younger age, higher BMI, and lack of chemotherapy (Table 1). Multiple systematic reviews further confirm that age and BMI are significant risk factors influencing the occurrence of incomplete OFS.[27–30]

Researchers conducted a systematic analysis of adolescent and young adult (AYA, aged 18–39 years) patients with HR+ breast cancer undergoing OFS treatment to identify predictors of incomplete OFS.[38] Results indicated that approximately half of the cohort exhibited E2 >20 pg/mL, signifying incomplete OFS, regardless of whether monthly or quarterly GnRHa administration was employed. These patients had a median age of 33.6 years and an average BMI of 29.2 kg/m^2, suggesting that younger age and higher BMI may be significant factors contributing to incomplete OFS.[38]

Another retrospective study involving 435 estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2−) breast cancer AYA patients demonstrated that patients aged ≤35 years had a higher rate of estrogen suppression failure compared to those aged 35–40 years. Age was identified as an independent risk factor for incomplete ovarian function suppression following OFS (P=0.002).[30] Additionally, a real-world data analysis yielded similar findings: multivariate analysis of age, BMI, and prior chemotherapy revealed that only age was statistically significantly associated with incomplete ovarian function suppression (P=0.024).[28] Another real-world study identified younger age as a potential risk factor for incomplete OFS (OR=0.900, 95% CI 0.824–0.982, P=0.018).[32]

Table 1 Summary of Clinical Studies Related to OE

Study	Sample Size	E2 Detection Methods	Definition of OE	OE Rate	Risk Factors
Lin et al, 2024[31]	1109	CLIA	E2 > 30 pg/mL;	6.3% (60/950)	Age; No prior chemotherapy
Chen et al, 2024[32]	264	ECLIA	E2 ≥ 30 pg/mL	7.2% (19/264)	Age
Tesch et al, 2024[33]	84	LC-MS/MS	E2 > 2.72 pg/mL	At 1 year: 54.7% (46/84); At 4 years: 60% (15/25)	No prior chemotherapy; TAM
Fleege et al, 2023[29]	131	ELISA or LC-MS/MS	E2 ≥ 10 pg/mL	Overall during treatment (cycle 2+): 26.7% (35/131) Within first 35 days (cycle 1): 24.1% (20/83) 1 year after OFS start: 9.2% (12/131)	/
Liu et al, 2022[30]	435	CLIA	E2 ≥ 10 pg/mL	5.5% (24/435)	Age
Burns et al, 2021[28]	46	LC-MS/MS	AI: E2 > 2.72 pg/mL; TAM: E2 > 21 pg/mL	3 months: 23.9% (11/46) 12 months: 6.5% (3/46)	Age
Dellapasqua et al, 2019[34]	51	GC/MS/MS	E2 > 2.72 pg/mL	Triptorelin + Letrozole group: 15.4% (4/26) Degarelix + Letrozole group: 0% (0/25)	/
Noguchi et al, 2016[35]	222	CLEIA	/	/	/
Bellet et al, 2016[27]	79	GC/MS/MS	E2 > 2.72 pg/mL (Exploratory threshold: >10 pg/mL, >20 pg/mL)	34.2% (27/79) had E2 > 2.72 pg/mL at least once (3 months: 25%, 6 months: 24%, 12 months: 17%)	No prior chemotherapy; BMI; lower FSH and LH
Aydiner et al, 2013[36]	79	RIA	E2 > 30 pg/mL	Leuprolide group: 12.2% (5/41) Goserelin group: 7.9% (3/38)	Age; No prior chemotherapy; No taxane use; cERB-B2 (HER2) positive tumors; Advanced tumor stage (T3+T4)
Masuda et al, 2011[37]	170	RIA	E2 > 30 pg/mL	Goserelin 10.8 mg group: 1.2% (1/86) Goserelin 3.6 mg group: 4.8% (4/84)	/

Abbreviations: ECLIA, Electrochemiluminescence immunoassay; CLIA, Chemiluminescence immunoassay; RIA, Radioimmunoassay; ELISA, Enzyme linked immunosorbent assay; GC/MS/MS, Gas chromatography tandem mass spectrometry; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; CLEIA, Chemiluminescent enzyme immunoassay.

The SOFT-EST study further investigated the clinical characteristics and baseline conditions of patients in the exemestane plus triptorelin treatment group who had at least one follow-up E2 level >2.72 pg/mL.[27] Compared to patients with E2 ≤2.72 pg/mL, these individuals exhibited significantly lower levels of luteinizing hormone (LH, P=0.004) and follicle-stimulating hormone (FSH, P=0.002), as well as higher BMI (P=0.05). Additionally, the absence of prior chemotherapy might also represent a potential risk factor for incomplete ovarian function suppression (P=0.06).

A real-world study demonstrated that individuals who achieved effective estrogen suppression during OFS combined with endocrine therapy typically had lower BMI (P<0.001), had undergone chemotherapy (P=0.002), and were relatively older (P=0.02).[29] In Lin et al's study, the incidence of incomplete ovarian function suppression was 6.3%, primarily occurring within the first 12 months of treatment. Risk factors for incomplete ovarian function suppression included age under 40 years (OR=4.67, P=0.003) and lack of prior chemotherapy (OR=3.16, P=0.001).[31] However, a real-world study utilizing multivariate logistic regression analysis found that low BMI was significantly associated with successful OFS within 35 days (P<0.05), while age and chemotherapy history did not demonstrate statistical significance.[29]

In Tesch et al's study, 54.7% of patients exhibited E2 levels >2.72 pg/mL after 1 year of treatment, and 60% after 4 years. Factors associated with this phenomenon included the absence of chemotherapy (P=0.045) and the use of tamoxifen (P=0.009). This may be attributed to tamoxifen's mixed agonist and antagonist effects, which can lead to increased estrogen levels.[33]

Although long-term OFS combined with endocrine therapy has been established as the standard adjuvant treatment strategy for HR+ breast cancer, the use of GnRHa does not guarantee that all patients will achieve postmenopausal status. Some patients may exhibit amenorrhea while still presenting persistently elevated serum E2 levels.[39] Achieving complete ovarian function suppression in premenopausal women undergoing OFS treatment is crucial to ensure the optimal efficacy of tamoxifen (TAM) and aromatase inhibitors (AIs). Aromatase inhibitors (AIs) reduce estrogen synthesis by inhibiting aromatase activity. However, incomplete ovarian suppression may allow the ovaries to continue producing estrogen, thereby counteracting the therapeutic effects of AIs. Furthermore, AIs may stimulate ovarian function, leading to increased ovarian estrogen production, which diminishes their efficacy. This may also exacerbate estrogen production through abnormal hypothalamic-pituitary feedback mechanisms, adversely affecting endocrine therapy outcomes.[40] Therefore, achieving complete and sustained ovarian function suppression is essential when combining GnRHa with AIs.

Systematic reviews have identified younger age and higher BMI as significant risk factors for ovarian escape in patients undergoing GnRHa treatment. Women under 40 years of age, due to stronger ovarian reserve function and higher baseline estradiol (E2) levels, are more likely to experience incomplete OFS.[31,41] Although patients under 35 years of age typically derive the greatest clinical benefit from OFS treatment, this population also faces a higher risk of incomplete ovarian function suppression.[42] Obesity promotes the expression of aromatase in adipose tissue through the "obesity-inflammation-aromatase axis," catalyzing the conversion of androstenedione and testosterone into estrone and estradiol, leading to elevated circulating estrogen levels.[43] Therefore, sensitive and continuous monitoring of serum E2 levels during the initial phase of GnRHa treatment and long-term follow-up is crucial for optimizing individualized endocrine therapy strategies and ensuring their efficacy.

Clinical Consequences of Ovarian Escape: What Risks Does It Pose?

In premenopausal breast cancer patients receiving OFS in combination with AI therapy, incomplete suppression raises two principal clinical concerns. First, restoration of estradiol to premenopausal levels may attenuate the antitumor efficacy of endocrine therapy, thereby compromising treatment outcomes. Second, AIs can paradoxically stimulate residual ovarian activity, potentially triggering ovulation and resulting in unintended pregnancy.[30] These consequences not only threaten disease control but may also impose additional physiological and psychological burdens on patients. Although large-scale prospective studies directly linking incomplete OFS to breast cancer recurrence are lacking, systematic reviews have suggested a possible adverse impact on clinical outcomes.[42,44] From a mechanistic standpoint, persistent or recurrent suboptimal suppression could cause fluctuations in circulating estrogen, theoretically increasing the risk of tumor recurrence.[28] However, current evidence does not conclusively demonstrate that ovarian escape (OE) significantly shortens disease-free survival (DFS) in premenopausal patients with hormone receptor–positive disease. Robust, long-term, multicenter studies are therefore warranted to clarify the prognostic implications of incomplete OFS and to guide optimal management strategies.

In a recent small systematic review on metastatic breast cancer (MBC), patients with incompleteOFS exhibited twice the incidence of overall survival (OS) events within one year of diagnosis compared to those with E2 ≤2.72 pg/mL (p = 0.052).[33] However, the impact of incomplete OFS on the clinical outcomes of MBC patients remains uncertain, necessitating further large-scale studies. A retrospective study conducted in China revealed that although patients with incomplete OFS generally had poorer prognoses, their disease-free survival (DFS) did not differ significantly from those with complete OFS.[30] These studies primarily investigated the potential impact of persistent incomplete OFS on prognosis. In clinical practice, however, transient elevations in E2 levels or isolated menstrual cycle abnormalities are more commonly observed. The SOFT-EST study demonstrated that the proportion of incomplete OFS decreased over time, with rates of 25%, 24%, and 17% at 3 months, 6 months, and 12 months, respectively.[27] Conversely, only 8% of patients exhibited persistent E2 levels >2.72 pg/mL. Another real-world study reported similar trends, with 6.3% of patients experiencing transient incomplete OFS within the first year of treatment, 55 cases occurring only once, and 5 cases occurring twice.[31] Notably, no cases of persistent incomplete OFS were observed during the 24-month treatment period. Furthermore, regardless of the formulation used, patients with transient or persistent incomplete OFS (P > 0.05) showed no significant differences in DFS and OS compared to those without incomplete OFS.[31] These findings suggest that the rate of incomplete OFS decreases over time, and patients experiencing transient incomplete ovarian function suppression exhibit no significant differences in prognosis compared to those without incomplete OFS.

In a meta-analysis of nine prospective trials, elevated levels of sex hormones, including E2, were found to double the risk of breast cancer recurrence in postmenopausal women.[45] Ingle et al employed liquid chromatography-tandem mass spectrometry (LC-MS/MS) to measure E2 and estrone (E1) levels in postmenopausal patients six months after receiving adjuvant aromatase inhibitor therapy.[46] Their results indicated that patients with serum E2 ≥0.5 pg/mL and E1 ≥1.3 pg/mL had a 2.25-fold increased risk of early breast cancer events compared to those with E1 and/or E2 below the respective thresholds. Another matched case-control clinical study demonstrated that E1 and E2 levels exceeding specific thresholds were significantly associated with the risk of early breast cancer events (EBCE) in postmenopausal women.[46] However, whether these findings are applicable to premenopausal breast cancer recurrence patients remains unclear.

Diagnosis and Clinical Management of Ovarian Escape

Currently, there is no standardized criterion for diagnosing ovarian escape, and existing clinical studies primarily rely on E2 level measurements for assessment. However, specific reference values have not been established, largely due to variations in detection instruments, reagents, and methodologies across different hospitals and laboratories. Additionally, the significant cyclical fluctuations in female sex hormone levels contribute to the lack of a unified standard for the timing of hormone level measurements. Other factors influencing result accuracy include endocrine therapy or targeted drug interventions during treatment, which may interfere with test outcomes. Therefore, in clinical practice, physicians should actively identify patients with high-risk characteristics or suggestive symptoms, such as resumption of menstruation, and implement stratified management strategies based on standardized monitoring and evaluation results (Figure 1).

Existing clinical studies commonly use serum E2 levels as the primary indicator for evaluating ovarian escape, given its critical role in reflecting ovarian function status. In the SOFT-EST subtrial, Smith et al's study, and Tesch et al's study, a strict threshold of 2.72 pg/mL was established for E2 levels to ensure precise evaluation of ovarian function suppression status.[27,33,40] However, other systematic reviews have adopted higher thresholds, such as 10, 20, or 30 pg/mL, which may be attributed to differences in study design and patient population characteristics.[31,47–49] Considering the stringent requirements for achieving complete ovarian function suppression during OFS combined with AI therapy, setting lower and stricter E2 level standards is particularly critical. Systematic reviews further highlight that when serum E2 levels are ≤2.72 pg/mL, this aligns with the significant reduction in estrogen secretion observed in the natural menopausal state of postmenopausal women, making this value the most appropriate and safe reference range during AI therapy.[10]

A prospective cohort study involving 84 HR+ breast cancer female patients undergoing OFS treatment with goserelin, leuprorelin, or triptorelin employed liquid chromatography-tandem mass spectrometry (LC-MS/MS) and standard assay methods to detect plasma estrogen levels.[50] The detection limit of LC-MS/MS was 0.2 pg/mL, with a threshold of 10 pg/mL. Results indicated that more than half of the patients exhibited incomplete OFS with E2 levels exceeding 2.72 pg/mL, and 91% of these patients had E2 levels undetectable by standard assay methods. At extremely low E2 concentrations,

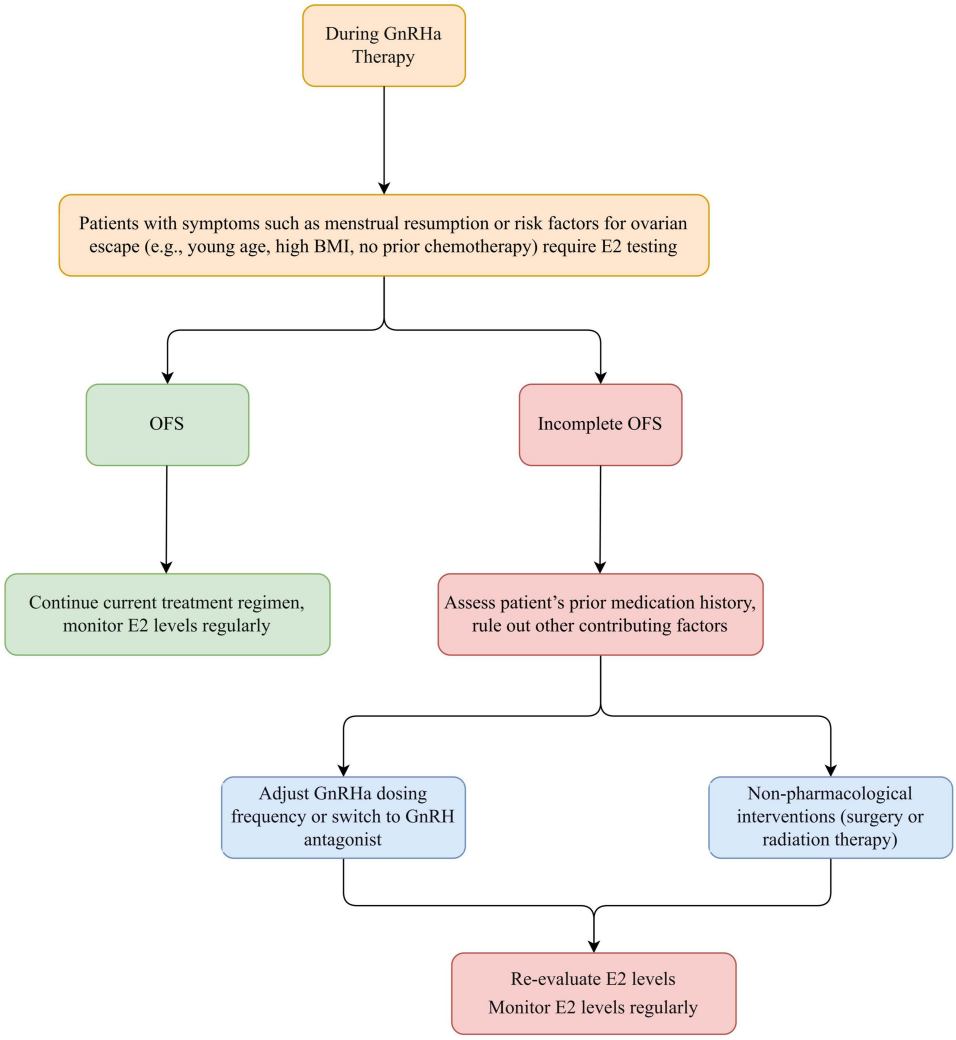

Figure 1 Algorithm for the Monitoring and Management of Ovarian Function During GnRHa Therapy in Premenopausal Breast Cancer.

traditional standard detection methods demonstrated insufficient sensitivity and accuracy, posing challenges for diagnosing incomplete OFS. Systematic reviews suggest that in studies conducted in developed countries, LC-MS/MS is recommended for precise quantification of E2 levels in breast cancer patients due to its superior sensitivity and specificity. In contrast, immunoassay methods exhibit lower sensitivity and specificity in such applications.[51–53] Nevertheless, immunoassays remain widely used due to their practicality and cost-effectiveness in various settings.[54] It is crucial to emphasize that inappropriate selection of assay methods may lead to erroneous evaluation of estradiol levels, resulting in incorrect treatment decisions.[55] Therefore, to minimize adverse outcomes caused by measurement bias and optimize treatment decisions, LC-MS/MS technology should be prioritized to enhance the accuracy and reliability of estradiol level assessment in monitoring OFS efficacy.

Additionally, several drugs used in breast cancer treatment may interfere with serum E2 measurement results. Fulvestrant and exemestane, due to their molecular structures being highly similar to 17β-estradiol, may affect estradiol detection results based on non-mass spectrometry techniques.[56–60] Abemaciclib, a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor approved for HR+ advanced breast cancer treatment, has been reported in clinical applications to occasionally cause elevated serum 17β-estradiol levels.[61,62]

Given the uncertainties in estradiol detection, more sensitive and convenient alternative monitoring indicators are being explored. A systematic review monitored serum gonadotropins, E2, and sex hormone-binding globulin (SHBG) concentrations in 135 patients, revealing a potential association trend between estradiol and SHBG ($r = -0.165$, $p =$

0.063) and FSH (r = −0.147, p = 0.088).[63] Researchers suggest that gonadotropin concentrations may serve as alternative indicators for BMI-related incomplete E2 suppression in routine monitoring. Furthermore, analysis from the prospective ABCSG-12 trial indicated that serum FSH levels during treatment could be a potential alternative parameter for evaluating the efficacy of OFS.[64] Studies also suggest that anti-Müllerian hormone (AMH) and inhibin B can predict ovarian reserve and recovery, with the RxPONDER trial emphasizing AMH as an important biomarker for defining ovarian reserve and predicting chemotherapy benefits in premenopausal HR+ breast cancer patients.[65–67]

For patients identified with incomplete OFS, a comprehensive assessment of treatment adherence should be conducted to determine whether incomplete suppression is due to non-compliance with scheduled GnRHa injections. Management strategies for incomplete OFS include switching GnRHa, using gonadotropin-releasing hormone antagonists, or adopting non-pharmacological interventions such as ovarian radiotherapy or oophorectomy.

Literature has reported three cases of ovarian escape in premenopausal hormone receptor-positive breast cancer patients receiving adjuvant AI and GnRHa therapy.[68] These patients exhibited incomplete ovarian function suppression during GnRHa treatment administered every three months, with clinical manifestations including menstruation, premenstrual syndrome, or ultrasound-detected follicular development. By adjusting the administration frequency from every three months to monthly, OFS improved in all three patients. Gupta et al reported a case where a patient experienced regular menstruation while using a three-month GnRHa formulation but achieved complete OFS after switching to a one-month GnRHa formulation.[39] A systematic review indicated that for patients with incomplete OFS caused by initial GnRHa, switching to other types or higher-frequency administration schemes resulted in complete OFS in half (n=7) of the cases.[69] However, despite similar case reports, definitive conclusions cannot be drawn due to small sample sizes. Additionally, more research data suggest that using GnRH agonists every three months is not inferior to monthly administration in achieving OFS.[28,31,32,35–37,70,71]

Switching to ovarian function suppression drugs such as GnRH antagonists is a feasible treatment strategy. In a systematic review by Silvia et al, patients treated with degarelix combined with letrozole achieved optimal OFS (defined as serum estradiol levels ≤2.72 pg/mL) faster than those treated with triptorelin combined with letrozole. Results showed that the degarelix group achieved optimal OFS three times faster than the triptorelin group. Furthermore, all patients in the degarelix group maintained optimal OFS during subsequent treatment cycles, whereas 15.4% of patients in the triptorelin group experienced ovarian escape (defined as serum estradiol levels >2.72 pg/mL) after the first treatment cycle, with 6 out of 127 measurements showing suboptimal OFS.[34] Coyne reported two cases of successful OFS achieved with the oral GnRH antagonist elagolix sodium in young patients who had experienced ovarian escape after using leuprorelin and goserelin.[19]

Surgical oophorectomy or radiotherapy represents alternative treatment options when drug-induced OFS fails. Consensus recommendations from the ERA project suggest that surgical oophorectomy or radiotherapy can be considered as alternatives when drug therapy proves ineffective.[72] In cases where drug-induced failure results in persistent ovarian escape, surgery or radiotherapy may serve as effective interventions. However, studies have shown that compared to surgical oophorectomy, approximately 20% to 30% of patients fail to achieve complete ovarian ablation following radiotherapy and may suffer damage to adjacent organs.[73,74] Considering that both treatment methods are permanent and irreversible, clinical decisions should prioritize patient preferences, particularly for young patients with fertility concerns. Physicians and patients should thoroughly evaluate economic costs, efficacy, and quality of life to determine the most appropriate course of action tailored to individual circumstances.

Summary and Outlook

Ovarian escape remains a significant and unresolved clinical challenge in the management of OFS, warranting increased attention. We have systematically reviewed the current evidence pertaining to ovarian escape and objectively highlighted a key feature of the existing literature: reported data on its incidence, risk factors, and clinical implications vary considerably and may even be contradictory. Such inconsistencies primarily arise from the absence of a gold standard definition, differences in the sensitivity of detection methods, and high heterogeneity among study populations. This underscores the lack of consensus in definition, monitoring protocols, and management approaches, which constitutes

a core challenge in clinical decision-making. To enhance diagnostic accuracy, multicenter, large-sample systematic reviews are essential for establishing more standardized and normalized criteria.

Future research should focus on refining optimal monitoring strategies, investigating more effective OFS drugs or treatment regimens, and developing biomarkers to predict ovarian escape risk. Pending the attainment of robust evidence-based consensus, cautious yet proactive management strategies should be adopted in clinical practice based on existing data. For high-risk groups, such as younger patients, individuals with elevated BMI, or those without prior chemotherapy, regular, sensitive monitoring is essential. Particularly, if patients undergoing OFS exhibit menstrual resumption, marked alleviation or disappearance of menopausal symptoms, or onset of premenstrual syndrome, ovarian escape should be strongly suspected. By identifying high-risk populations, implementing regular monitoring, and adopting effective interventions, treatment outcomes can be optimized, and patient prognosis improved.

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Disclosure

The authors declare that they have no conflict of interest.

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