Adverse Effects of Ovarian Suppression and Endocrine Therapy in Patients with Breast Neoplasms: Integrative Literature Review

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Efeitos Adversos da Supressão Ovariana e da Terapia Endócrina em Pacientes com Câncer de Mama: Revisão Integrativa da Literatura

Efectos Adversos de la Supresión Ovárica y la Terapia Endocrina en Pacientes con Neoplasias de la Mama: Revisión Integradora de la Literatura

Gabrielle Negrão Amorim[1]; Maria Cláudia Bernardes Spexoto[2]

ABSTRACT

Introduction: Breast cancer is the most common neoplasm among women worldwide and represents a major public health issue. Endocrine therapy (ET) and ovarian function suppression (OFS) are fundamental strategies in the treatment of hormone-sensitive tumors; however, they are associated with adverse effects that may impact quality of life and treatment adherence. **Objective:** To identify the main adverse effects associated with ET and OFS in patients with breast cancer, analyzing their impact on quality of life and treatment adherence. **Method:** Integrative literature review, structured according to the PRISMA 2020 recommendations, with methodological adaptations. The search was conducted in February 2025 in PubMed, Scopus, and Web of Science using a PICo-based strategy. Observational studies and clinical trials published between 2015 and 2025 were included. Study selection was performed using the Rayyan software, with screening of titles, abstracts, and full-text assessment of eligible articles. **Results:** The final sample consisted of eight studies. Evidence indicates that ET and OFS are associated with physical, metabolic, sexual, psychological, and oral adverse effects, including hot flashes, fatigue, insomnia, weight gain, sexual dysfunction, and emotional changes. These effects may impair quality of life and reduce treatment adherence, particularly in combined therapies. **Conclusion:** Adverse effects associated with ET and OFS are multifactorial and clinically relevant and may negatively impact quality of life and treatment continuity.

Key words: Breast Neoplasms/drug therapy; Antineoplastic Agents, hormonal/adverse effects; Drug-Related Side Effects and Adverse Reactions; Quality of life.

RESUMO

Introdução: O câncer de mama é a neoplasia mais incidente entre mulheres em nível mundial, representando importante problema de saúde pública. A terapia endócrina (TE) e a supressão da função ovariana (SFO) são estratégias fundamentais no tratamento de tumores hormônio-sensíveis, porém estão associadas a efeitos adversos que podem impactar a qualidade de vida e a adesão ao tratamento. **Objetivo:** Identificar os principais efeitos adversos associados à TE e à SFO em pacientes com câncer de mama, analisando seu impacto na qualidade de vida e na adesão ao tratamento. **Método:** Revisão integrativa da literatura, estruturada conforme as recomendações do PRISMA 2020, com adaptações metodológicas. A busca foi realizada em fevereiro de 2025 nas bases *PubMed, Scopus* e *Web of Science*, utilizando estratégia baseada em PICo. Foram incluídos estudos observacionais e ensaios clínicos publicados entre 2015 e 2025. A seleção dos estudos foi realizada por meio do *software Rayyan*, com triagem por títulos, resumos e avaliação dos artigos elegíveis na íntegra. **Resultados:** A amostra final foi composta por oito estudos. As evidências indicam que a TE e a SFO estão associadas a efeitos adversos físicos, metabólicos, sexuais, psicológicos e bucais, incluindo ondas de calor, fadiga, insônia, ganho de peso, disfunção sexual e alterações emocionais. Esses efeitos podem comprometer a qualidade de vida e reduzir a adesão ao tratamento, especialmente em terapias combinadas. **Conclusão:** Os efeitos adversos associados à TE e à SFO são multifatoriais e clinicamente relevantes, podendo impactar a qualidade de vida e a continuidade do tratamento.

Palavras-chave: Neoplasias da Mama/ tratamento farmacológico; Antineoplásicos Hormonais/efeitos adversos; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Qualidade de Vida.

RESUMEN

Introducción: El cáncer de mama es la neoplasia más frecuente entre las mujeres a nivel mundial y representa un importante problema de salud pública. La terapia endocrina (TE) y la supresión de la función ovárica (SFO) son estrategias fundamentales en el tratamiento de tumores hormonosensibles, sin embargo están asociadas a efectos adversos que pueden afectar la calidad de vida y el compromiso con el tratamiento. **Objetivo:** Identificar los principales efectos adversos asociados a la TE y la SFO en pacientes con cáncer de mama, analizando su impacto en la calidad de vida y el compromiso con el tratamiento. **Método:** Revisión integradora de la literatura, estructurada de acuerdo con las recomendaciones de PRISMA 2020, con adaptaciones metodológicas. La búsqueda se realizó en febrero de 2025 en las bases de datos PubMed, Scopus y Web of Science, utilizando una estrategia basada en PICo. Se incluyeron estudios observacionales y ensayos clínicos publicados entre 2015 y 2025. La selección de los estudios se realizó mediante el *software* Rayyan, filtrando por títulos, resúmenes y evaluación de texto completo de los artículos elegibles. **Resultados:** La muestra final estuvo compuesta por ocho estudios. La evidencia indica que la TE y la SFO están asociadas a efectos adversos físicos, metabólicos, sexuales, psicológicos y bucales, incluidos bochornos, fatiga, insomnio, aumento de peso, disfunción sexual y alteraciones emocionales. Estos efectos pueden comprometer la calidad de vida y reducir el compromiso con el tratamiento, especialmente en terapias combinadas. **Conclusión:** Los efectos adversos asociados a la TE y la SFO son multifactoriales y clínicamente relevantes, pudiendo afectar la calidad de vida y la continuidad del tratamiento.

Palabras clave: Neoplasias de la Mama/tratamiento farmacológico; Antineoplásicos Hormonales/efectos adversos; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Calidad de Vida.

[1]Universidade Federal da Grande Dourados (UFGD), Faculdade de Ciências da Saúde (FCS). Dourados (MS), Brasil. E-mails: gabrielle.amorim053@academico.ufgd.edu.br; gabriele-negrao@outlook.com. Orcid iD: https://orcid.org/0009-0007-2699-8517

[2]UFGD, FCS, Programa de Pós-Graduação em Alimentos, Nutrição e Saúde (PPGANS). Dourados (MS), Brasil. E-mail: mariaspexoto@ufgd.edu.br. Orcid iD: https://orcid.org/0000-0001-7681-1422

Corresponding author: Gabrielle Negrão Amorim. Rua Casimiro de Abreu, 415 – Jardim dos Cristhais. Dourados (MS), Brasil. CEP 79821-026. E-mail: gabriele-negrao@outlook.com

INTRODUCTION

Breast cancer is the most common neoplasm among women worldwide, being a serious public health issue[1]. In Brazil, official estimates by the National Cancer Institute (INCA) indicate that in the 2026-2028 period there will be approximately 79 thousand new cases a year, being the main cause of cancer mortality in women in the country[2]. The therapeutic management of breast cancer is complex and based on biological, genetic, and histopathological characteristics, which directly influence clinical decision-making. Diagnosis is confirmed by biopsy of the suspicious lesion, with histopathological and immunohistochemical analysis of hormone receptors (estrogen and progesterone receptors) and HER2 receptors, fundamental for molecular classification and definition of the most appropriate therapy[3]. Additionally, around 65% to 80% of breast tumors in women in pre-menopause are classified as luminal tumors of the positive hormonal receptor type (HR+), characterizing a group with greater sensitivity to endocrine therapy (ET)[4].

To slow down the growth of hormone-dependent tumoral cells, ET and ovarian function suppression (OFS) are therapeutic strategies indicated to reduce the availability of estrogen for the tumoral cell[5]. OFS can be reversed using gonadotropin-releasing hormone (GnRH) analogues, like triptorelin and goserelin, or, permanently, through bilateral oophorectomy (surgical ablation) or induced by pelvic radiotherapy[6]. In premenopausal patients with HR+ metastatic breast cancer, OFS constitutes a fundamental step in hormonal blockade, frequently associated with systemic ET to optimize disease control[7].

Despite the consolidated efficacy of ET and OFS in reducing recurrence and improving survival in patients with breast cancer, prolonged hormonal blockade is associated with different adverse effects that may significantly compromise the quality of life of patients. The national and international literature has a gap in systematizing the impact of these effects on treatment adherence, especially for young women, who have been increasingly targeted by breast cancer. In light of this, it becomes relevant to map out these clinical repercussions to support early symptom management strategies within the National Health System (SUS) context, contributing to improved therapy adherence and clinical outcomes.

The objective of this study is to identify the main adverse effects associated with ET and OFS in patients with breast cancer, analyzing their impact on quality of life and treatment adherence.

METHOD

Integrative literature review developed to synthesize the evidence available on the adverse effects of ET and OFS in patients with hormone-sensitive breast cancer, as well as their impacts on the quality of life and treatment adherence. In this study, a methodological analysis was conducted following the six steps proposed by Sousa et al.[7]: 1) Definition of the theme and formulation of the research question; 2) criteria for inclusion and exclusion of studies; 3) identification of information to be collected; 4) assessment of the selected studies; 5) interpretation of results; and 6) presentation of synthesis of knowledge.

The research question was structured following the PICo strategy, used for studies that focus on phenomena of interest. In this strategy, P (Population) corresponds to women with hormone-sensitive breast cancer; I (Interest) to the adverse effects related to ET and OFS; and Co (Context) to the impacts of these events on quality of life and treatment adherence. Based on this structure, the research question of this review consisted of identifying the main adverse effects associated with ET and OFS in patients with breast cancer and analyzing their repercussions on quality of life and treatment adherence.

Studies were searched in the National Library of Medicine (PubMed), Scopus, and Web of Science databases in February 2025. For PubMed, the following search strategy was used: (*breast neoplasms* AND *antineoplastic agents, hormonal* AND *adverse effects* AND *quality of life*). For Scopus and Web of Science, the following terms were searched: *breast cancer, endocrine therapy, suppression of ovarian function, adverse effects*, and *quality of life*, with the Boolean operator AND added between the words in the advanced search.

The inclusion criteria were articles published between 2015 and 2025, indexed in the chosen databases and available for full reading, articles written in English, and classified as clinical trials or observational studies. The exclusion criteria were duplicate articles, inconclusive or incomplete articles, other literature reviews, case reports, editorials, letters to the editor, and publications that did not answer the research question.

The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[8] guidelines. Initially, all studies were exported to the *Rayyan*[9] software, used for the identification and removal of duplicates and for screening articles by reading titles and abstracts. Later, the potentially eligible studies were submitted to full reading for confirmation of eligibility, and only those that fully met the previously established criteria were included.

The choice of an integrative review is justified by the possibility of synthesizing evidence from different methodological designs, including observational studies and clinical trials, enabling a broad, structured analysis of complex phenomena related to the adverse effects of ET and OFS in breast cancer.

For each included study, data referring to publication year, country, methodological design, sample characteristics, outcomes related to adverse effects, quality of life, and treatment adherence were extracted. Data was organized in comparative tables for the systematization of the findings.

The results were interpreted through narrative synthesis and comparative analysis between the included studies. Due to the heterogeneity in methodologies, populations, and outcomes, it was not possible to conduct a meta-analysis.

RESULTS

The database search initially retrieved 2,017 manuscripts (PubMed: 306; Scopus: 1,692; Web of Science: 19). Of that total, 1,806 records were eliminated by the automated filtering step due to language restrictions, publication period, full-text unavailability, or incompatibility with the eligible study design (clinical trials and observational studies). Of the 211 remaining articles processed in the *Rayyan* software, 5 were identified and removed as duplicates, leaving 206 records for screening of titles and abstracts. The initial assessment excluded 166 articles that did not address the proposed theme. Next, 40 articles were selected for full reading, of which 32 were discarded for not meeting the predefined eligibility criteria or not directly addressing the objective of this review. The final sample consisted of 8 indexed articles, as detailed in the illustrated methodological flowchart (Figure 1). The synthesis of the main characteristics of each selected article was grouped in Chart 1.

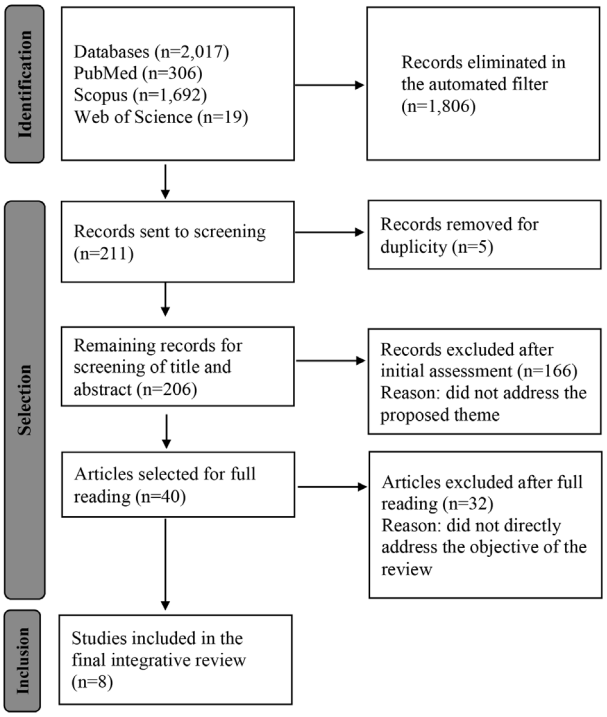

Figure 1. PRISMA flowchart of article selection
Source: Adapted from PRISMA[8].

DISCUSSION

The subjects addressed by the articles were subdivided into two categories for better organization and understanding of the results: 1) Studies that compared ET and/or OFS with other treatments and/or placebo; 2) Studies that analyzed different ET modalities and/or compared OFS methods. This categorization was elaborated from the methodological characteristics and objectives of the included studies, enabling a more systematic analysis of the findings. The association between the utilized drugs, their respective adverse effects, the impact on quality of life, and the outcome of therapy adherence are summarized in Chart 2. It is worth noting that the findings were analyzed in a comparative and integrated manner across the studies, enabling the identification of recurring patterns of adverse effects associated with different therapeutic modalities.

CATEGORY 1 – STUDIES THAT COMPARED ET AND/OR OFS TO OTHER TREATMENTS AND/OR PLACEBO

The longitudinal study conducted by Ferreira et al.[11], which followed 4,262 patients for two years after the breast cancer diagnosis, concluded that patients who had undergone just chemotherapy had a more transitory negative impact when compared to patients who used ET, who, in turn, had a prolonged negative effect. The analysis of this study indicates that patients who underwent ET have worse side effects and worse quality of life when compared to those submitted to just chemotherapy, affecting the overall health status and social function of these patients. The study also discusses that the choice of medication, whether tamoxifen or an aromatase inhibitor, may have influenced the results, especially in the worst quality of life outcome observed in post-menopausal women. Additionally, ET showed a negative impact on aspects such as social function and participation, pain, insomnia, and breast symptoms, in addition to further compromising emotional function and recovery of the future perspective. Although the study did

Chart 1. General characteristics and design of the selected studies

Title	Author	Year	Country of origin	Sample (n) and clinical profile	Design/Intervention
Quality of life in women with early-stage and metastatic hormone receptor-positive, HER2-negative breast cancer receiving endocrine therapy	O'Reilly et al.[10]	2024	Ireland	417 patients (331 with disease in initial stage and 86 with metastatic disease)	Cross-sectional observational study; quality of life assessment in ET regimen
Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis	Ferreira et al.[11]	2019	France	4,262 patients (37.2% pre-menopause, 62.8% post-menopause). 81.9% in ET; 52.8% in chemotherapy	Multicentric prospective study; comparison between ET, chemotherapy, and combined therapy regarding quality of life
Efficacy and safety of leuprorelin acetate 6-month depot, TAP-144-SR (6M), in combination with tamoxifen in postoperative, premenopausal patients with hormone receptor-positive breast cancer: a phase III, randomized, open-label, parallel-group comparative study	Kurebayashi et al.[12]	2016	Japan	167 premenopausal patients (83 received leuprorelin with a 6-month depot and 84 with a 3-month depot)	Randomized clinical trial, phase III, open; comparative of parallel groups
Tooth loss in breast cancer patients: A comparison between tamoxifen-treated and non-treated patients	Julca-Baltazar et al.[13]	2024	Peru	200 patients (100 using tamoxifen and 100 without hormonal treatment)	Comparative cross-sectional study; comparison of tooth loss in patients treated with and without tamoxifen
A prospective, randomized study of Toremifene vs. tamoxifen for the treatment of premenopausal breast cancer: safety and genital symptom analysis	Hong et al.[14]	2020	China	104 premenopausal patients (52 using toremifene and 52 using tamoxifen)	Open, randomized clinical trial of parallel groups; comparative analysis of genital symptoms and safety
Treatment-induced symptoms, depression and age as predictors of sexual problems in premenopausal women with early breast cancer receiving adjuvant endocrine therapy	Ribi et al.[15]	2020	Switzerland	2,287 selected premenopausal patients (of the global 5,738 cohort) distributed across 5 cohorts (isolated ET, combined OFS, and chemotherapy regimens)	Observational cohort; comparison between isolated ET and ET associated with OFS
Major depressive symptoms in breast cancer patients with ovarian function suppression: a cross-sectional study comparing ovarian ablation and gonadotropin-releasing hormone agonists	Jiang et al.[16]	2021	China	563 patients submitted to OFS (174 to surgical ablation and 389 to analogue GnRH)	Comparative cross-sectional study on the prevalence of greater depressive conditions according to the type of OFS
Factors associated with weight gain in pre- and post-menopausal women receiving adjuvant endocrine therapy for breast cancer	Uhelski et al.[17]	2023	USA	309 patients included in the final analysis (99 premenopausal and 210 post-menopausal). Of those, 132 with tamoxifen ± OFS; 177 with aromatase inhibitors ± OFS	Retrospective observational study; assessment of factors associated with weight gain during adjuvant ET

Captions: ET = endocrine therapy; OFS = ovarian function suppression; GnRH = gonadotropin-releasing hormone.

Chart 2. Synthesis of adverse effects, impacts on quality of life, and treatment adherence identified in the included studies

Author (Year)	Assessed treatment	Main adverse effects	Impact on quality of life	Impact on treatment adherence
O'Reilly et al.[10] (2024)	ET in initial and metastatic cancer	Endocrine symptoms related to the treatment	Negative impact on quality of life, especially in patients with initial disease	Patients with cancer in the initial stage presented higher rates of treatment discontinuity
Ferreira et al.[11] (2019)	ET (tamoxifen or aromatase inhibitors)	Pain, insomnia, endocrine symptoms, and breast symptoms	Reduced overall health status, emotional function, and social participation	Prolonged adverse effects were suggested as potential factors related to lower prolonged treatment adherence
Kurebayashi et al.[12] (2016)	Leuprorelin with a 3-month versus 6-month depot	Hot flashes, cephalalgia, weight gain, and insomnia	Reduced physical comfort from adverse events	Not directly assessed
Julca-Baltazar et al.[13] (2024)	Tamoxifen	Xerostomia, burning sensation in the mouth, and tooth loss	Impaired oral comfort and physical well-being	Not directly assessed
Hong et al.[14] (2020)	Tamoxifen versus toremifene	Ovarian cysts, endometrial thickening, and hepatic steatosis	Potential impact from gynecological and metabolic alterations observed	Not directly assessed
Ribi et al.[15] (2020)	ET with or without OFS	Vaginal dryness, bone and joint pain, hot flashes, and sleep disorders	Relevant clinical worsening of sexual function during the first two years of treatment	Persistent symptoms may compromise therapeutic continuity, especially when ET is associated with OFS
Jiang et al.[16] (2021)	GnRH agonists versus OFS	Higher depressive symptoms after OFS	Worsening mental health, mainly among patients subjected to OFS	Not directly assessed
Uhelski et al.[17] (2023)	Adjuvant ET	Weight gain, sleep disorders, fatigue, anxiety, and depression	Compromised physical and emotional well-being	More intense endocrine symptoms were associated with worse therapeutic experience

Captions: ET = endocrine therapy; OFS = ovarian function suppression; GnRH = gonadotropin-releasing hormone.

not directly assess therapeutic interruption, its findings suggest that these persistent symptoms may represent a barrier to treatment continuity. In the context of SUS, in which ET is often maintained for prolonged periods, the systematic follow-up of adverse effects may contribute to minimizing the impact on quality of life and favor therapy adherence. In general, this set of findings reinforces that ET is associated with a prolonged symptomatic burden when compared to other therapeutic modalities.

Regarding oral adverse effects, the study by Julca-Baltazar et al.[13] established a direct association between the prolonged use of tamoxifen (for longer than one year) and the prevalence of tooth loss in adult women. The study also suggests this effect may be related to estrogen deficiency, since reduced estrogen levels tend to compromise salivary flow, decreasing oral pH and favoring gingival inflammatory processes, cavities, and dental attachment loss, in addition to symptoms like xerostomia and oral burning sensation. These alterations may compromise the comfort and well-being of patients, negatively affecting quality of life. The findings also demonstrate that adverse effects of ET are not limited to the vasomotor and musculoskeletal symptoms frequently described in the literature and can affect different healthcare dimensions. In this context, including preventive dental follow-up in oncology services may contribute to early identification and management of these alterations during treatment, given that these symptoms cause great continuous physical discomfort, which reflects on general well-being.

Analyzing the metabolic impact of adjuvant ET, Uhelski et al.[17] demonstrated that clinically significant weight gain (≥5%) affects a significant portion of patients in treatment, demonstrating an intimate association with the intensity of early endocrine symptoms. The study weighs in that menopause induced by hormonal blockade drastically alters fat distribution and body composition in women, working in association with other frequently observed factors, such as persistent sleep disorders, chronic fatigue, anxiety, and depression[17]. Together, these metabolic and psychological alterations

can compromise the physical and emotional well-being of patients, negatively affecting quality of life and treatment experience. The overlap of these metabolic and psychic symptoms may represent a barrier to therapy continuity, especially when associated with greater intensity of endocrine symptoms.

CATEGORY 2 – STUDIES THAT ANALYZED DIFFERENT MODALITIES OF ET AND/OR COMPARED OFS METHODS

When assessing the impact of combined or isolated regimens on the sexual function of women in pre-menopause, Ribi et al.[15] identified a progressive and clinically relevant worsening in the sexual problem indices over two years of follow-up in all the analyzed cohorts. This deterioration was significantly sharper and earlier (beginning in the first six months) in patients who underwent ET associated with OFS than in those in hormonal monotherapy, with one of the main clinical predictors of this outcome being vaginal dryness, bone/joint pain, and sleep disorders[15]. These findings suggest that the association between ET and OFS is related to a higher symptomatic burden, especially in the sexual health scope, with a potential impact on quality of life during the treatment. Together, the combined schemes tend to present a greater negative impact on sexual function when compared to hormonal monotherapy, which can impact treatment continuity in the long term.

Regarding treatment perception according to disease prognosis, David O'Reilly[10] assessed the impact of ET comparing women with initial and metastatic disease. The findings revealed that patients in the initial stages, despite the healing potential of the treatment, reported a greater burden of endocrine symptoms and showed higher rates of medication discontinuity in relation to metastatic patients. The authors suggest that the perception of treatment benefits and perspectives of the disease may influence how adverse effects are experienced by patients. The lower tolerability observed in the initial stage indicates that this group is more vulnerable to non-adherence. This finding suggests a possible influence of risk-benefit perception on therapy adherence.

Kurebayashi et al.[12] studied two groups of patients in OFS, both using leuprorelin, with three- and six-month application intervals. Although the efficacy profile is comparable, the study reported that systemic adverse events, including hot flashes, cephalalgia, weight gain, and insomnia, tend to be slightly more prevalent and reported by patients exposed to the six-month application regimen. The greater occurrence of these events suggests the need for regular clinical follow-up, considering their potential impact on physical comfort and daily activities.

In directly comparing selective modulators of the estrogen receptor, the prospective trial by Hong et al.[14] demonstrated comparable safety and toxicity profiles between the use of toremifene and tamoxifen in premenopausal women. Both interventions exhibited expressive rates of gynecological and hepatic complications, characterized by a high incidence of ovarian cysts, endometrial wall thickening, and development of hepatic steatosis over a year of monitoring, with no statistical differences that justify absolute superiority of one drug over another[14]. These findings reinforce the importance of clinical and laboratory monitoring during treatment, aiming at early identification and proper management of possible complications.

In the mental health panorama, Jiang et al.[16] compared the effects of temporary OFS via GnRH analogue/agonists *versus* definitive OFS. The results evidenced that young survivors who underwent definitive OFS procedures or mutilating surgical procedures, like mastectomy, presented a significantly higher probability of developing greater depression and sexual dysfunction, correlating this psychic impact to the abrupt and irreversible transition to menopause state[16]. These results reinforce the relevance of psychosocial aspects in the follow-up of patients since persistent emotional alterations can compromise the quality of life and impair treatment continuity.

Finally, it must be considered that these findings have important limitations. Most selected studies presented an observational or cross-sectional design, which impairs the establishment of a direct cause-and-effect relationship between hormonal blockade and the reported symptoms. Furthermore, many results were obtained through self-reporting instruments, making the assessments susceptible to the subjectivity of participants regarding the perception of symptoms, quality of life, and emotional health. Another relevant aspect refers to the heterogeneity of the included studies, which differed regarding the assessed populations, therapeutic modalities, and investigated outcomes. Therefore, the reviewed evidence must be interpreted as clinical associations that signal important trends for practical management of adverse effects in SUS, and not as absolute causal rules.

CONCLUSION

This integrative review demonstrated that ET and OFS are associated with different physical, metabolic, sexual, psychological, and oral adverse effects, which may negatively impact the quality of life of patients with breast cancer. The most frequently reported symptoms include hot flashes, insomnia, fatigue, weight gain, vaginal dryness, emotional alterations, and oral manifestations.

The findings suggest that a higher symptomatic burden, especially in the association between ET and OFS, may impair therapy continuity and influence treatment adherence for some patients. In this context, multiprofessional follow-up with psychological, nutritional, and dental support may contribute to managing adverse effects and maintaining quality of life during the treatment.

As limitations, we observe that, although there is a diversity of studies on the theme, most of them do not directly compare patients in ET or OFS with unexposed groups, nor consistently assess the relationship between adverse effects and therapeutic adherence. Moreover, observational studies predominate, with frequently self-reported measurements and great methodological heterogeneity, which limits comparability between results and impairs more robust causal inferences. This gap in the literature impairs a precise comparative analysis of quality of life and side effects associated with these treatments.

Thus, the results of this review may be interpreted as evidence of clinical association, and not as a demonstration of causality. In this context, we highlight the need for prospective studies with longitudinal follow-up and well-defined comparative groups to enable more consistent comparisons between different therapeutic groups.

CONTRIBUTIONS

Gabrielle Negrão Amorim has contributed to the study design and planning, data acquisition, analysis and interpretation, wording, and critical review. Maria Cláudia Bernardes Spexoto has contributed to the wording and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the contents associated with the article are included in the manuscript.

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