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# Impact of trastuzumab on Anti-Müllerian (AMH) levels in patients undergoing (neo) adjuvant treatment for breast cancer: a systematic review

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## Abstract

**Background:** Trastuzumab is a monoclonal antibody targeting HER2, overexpressed in approximately 25%–30% of breast cancers. While its survival benefit is well established, its impact on ovarian function and fertility preservation remains uncertain in premenopausal women.

**Methods:** A systematic literature review was conducted using MEDLINE and Biblioteca Virtual em Saúde databases, covering publications from 2010 to January 2025. Eligible studies included phase II–III clinical trials, prospective and retrospective observational studies and systematic reviews evaluating ovarian function outcomes – particularly amenorrhea rates and anti-Müllerian hormone (AMH) levels – in women with HER2-positive breast cancer treated with trastuzumab in the (neo)adjuvant setting.

**Results:** Eleven studies met the inclusion criteria: eight prospective, two retrospective and one descriptive. Four studies reported no association between trastuzumab and increased amenorrhea rates, one suggested higher amenorrhea when combined with chemotherapy and four demonstrated lower amenorrhea rates along with preservation of AMH levels, suggesting a potential protective effect on ovarian reserve. Two studies did not directly assess amenorrhea.

**Conclusion:** Current evidence does not demonstrate a consistent gonadotoxic effect of trastuzumab. Although some data suggest a possible protective role on ovarian function, findings remain heterogeneous. Prospective studies specifically designed to isolate the ovarian impact of trastuzumab are warranted. Comprehensive oncofertility counseling should be offered to all premenopausal women before treatment initiation.

**Keywords:** *breast cancer*, *HER2-positive*, *trastuzumab*, *anti-Müllerian hormone*, *ovarian reserve*, *systematic review*

Review

## Introduction

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related death in women under the age of 40. While incidence rates have stabilised in older populations, they continue to rise among younger women [1]. For this demographic, ovarian toxicity is a primary concern, as chemotherapy can lead to irreversible adverse effects, including premature ovarian failure and infertility, which carry long-term

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implications for bone density, cardiovascular health and cognitive function [1]. Consequently, international guidelines emphasize that gonadotoxicity must be discussed with all patients of childbearing age before initiating treatment [2].

To monitor ovarian damage and recovery, clinical practice relies on surrogate markers such as anti-Müllerian hormone (AMH) [2]. Secreted by early-stage follicles, AMH is a highly reliable indicator of ovarian reserve because its serum concentrations remain stable throughout the menstrual cycle [3]. Assessing AMH levels post-chemotherapy is essential for determining the immediate degree of follicular toxicity and the potential for long-term functional recovery [3].

While the gonadotoxicity of traditional chemotherapeutic agents is well documented, the effects of newer targeted therapies on ovarian function remain less well characterized and are the subject of increasing investigation [4, 8, 9]. Trastuzumab is a monoclonal antibody directed against the HER2 receptor, blocking HER2-mediated signaling pathways involved in cell proliferation and survival [4, 10]. HER2 is also expressed in a subset of normal ovarian cells, supporting the biological plausibility that HER2 inhibition could influence ovarian physiology [5, 11].

Despite trastuzumab's established role in significantly reducing recurrence and mortality in HER2-positive breast cancer, its specific impact on fertility and ovarian reserve is not yet fully understood [6–9]. Given this uncertainty and the rising incidence of breast cancer in younger women, this systematic review aims to synthesize the existing evidence regarding the impact of trastuzumab on ovarian function and AMH levels [6].



## Methods

This systematic review was conducted according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was not prospectively registered in PROSPERO or any other systematic review registry.

Data management, including the tracking of the study selection process and the generation of the PRISMA flow diagram (Figure 1), was performed using Microsoft Excel software.

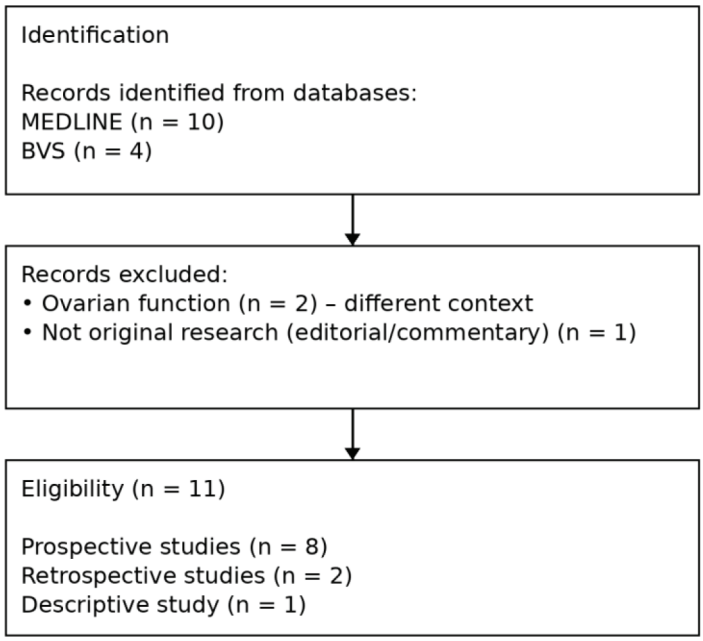


**Figure 1. PRISMA flow diagram.**

We searched for records published from 2010 to January 2025, reporting outcomes related to ovarian function in women with HER2-positive breast cancer undergoing (neo) adjuvant treatment with trastuzumab. Randomised clinical trials (phase II or phase III), systematic reviews with or without meta-analysis, prospective and retrospective observational studies were considered eligible. Phase I/II trials were included only if the results of the phase II part could be extrapolated.

To this purpose, the following terms and their synonyms were variously combined in a search string: breast cancer, HER2-positive, trastuzumab, chemotherapy, amenorrhea, ovarian function, fertility, AMH, menstrual function, gonadotoxicity, ovarian reserve and (neo)adjuvant treatment. The search strategy employed relevant medical subject headings to ensure comprehensive retrieval of pertinent literature.

Full-length articles and published conference abstracts were considered. Reviews, editorials, commentaries and case reports/series were excluded. Only publications written in English or Portuguese were eligible, as translation resources were not available. The literature search was performed in MEDLINE via PubMed and Biblioteca Virtual em Saúde. All searches were performed until the first week of January 2025.

After duplicate removals, two authors (RMS and CF) independently screened the titles and abstracts of each record. Controversies were resolved by a third author (JB). The full texts of selected records were then assessed for eligibility using the same procedure.

Studies' features and results, including amenorrhea rates and ovarian function markers, were independently extracted in an electronic database by two authors (RMS and GARM). Reported outcomes included at least one of the following markers: amenorrhea rate assessed through questionnaire or clinical interview, laboratory analysis (including AMH, FSH and estradiol levels) or ultrasound evaluation for antral follicle count assessment. Studies that did not report ovarian function outcomes were excluded to ensure that only evidence specific to the research question was included. Additionally, we explored data on baseline characteristics and treatment regimens reported in the included studies to identify factors potentially associated with differential effects on ovarian function.

Due to the heterogeneity of the included studies in terms of study design, treatment regimens, outcome measures and follow-up duration, a narrative synthesis of the available evidence was conducted to summarise and report the findings rather than a quantitative analysis (meta-analysis). Moreover, we did not perform risk-of-bias assessment using standardised tools (e.g., Cochrane Risk of Bias or ROBINS-I), as the primary objective was to provide a comprehensive overview of the existing evidence on this emerging topic rather than to grade the quality of individual studies. The heterogeneity across study designs and outcome definitions would have limited the applicability and interpretability of such assessments.



## Results

A total of 11 studies met the inclusion criteria for this systematic review.

Eight prospective studies evaluating trastuzumab-associated amenorrhea were included [13–15, 17–18, 21–23] along with two retrospective studies addressing the same outcome [16, 19].

Additionally, one descriptive study providing information on oncofertility among women with HER 2-positive breast cancer was identified [20].

The total number of participants across the cited trials with available information is 6.357, summing the explicit counts from the studies described in Table 1.

All the studies evaluated gonadotoxicity associated with treatment regimens in HER2-positive breast cancer, with a focus on the impact of trastuzumab-containing therapies on amenorrhea and ovarian function.

In summary: several prospective studies reported no consistent increase in amenorrhea attributable to trastuzumab when added to standard chemotherapy, suggesting no substantial gonadotoxicity attributable to trastuzumab alone. These include the Adjuvant Paclitaxel and Trastuzumab (APT) trial [13], the NRG/NSABP B-47 menstrual history study [14] and the ATEMPT trial [15].

Some retrospective analyses and exploratory analyses highlighted that amenorrhea rates vary with regimen intensity and concomitant treatments; for example, ALTTO exploratory analysis [16] and Abusief *et al* [19] show amenorrhea rates within ranges expected given concurrent

chemotherapy, with trastuzumab not consistently increasing gonadotoxicity. Additional supporting data come from Morarji *et al* [22] on ovarian function after chemotherapy with/without trastuzumab, and Poorvu *et al* [23] on treatment-related amenorrhea in a modern prospective cohort with regimens including trastuzumab ± pertuzumab.

**Table 1. Clinical trials evaluating gonadotoxicity in patients with HER2-positive breast cancer.**

| Author (Year) | No. of participants | Title/Trial | Study type | Treatment scheme | Main findings/ Conclusion |
|---|---|---|---|---|---|
| Ruddy *et al* (2015) [13] | 410 | CRA after APT trial | Prospective | Paclitaxel + trastuzumab | Amenorrhea rates were lower than those historically reported with alkylating-based regimens. |
| Ganz *et al* (2021) [14] | 1,231 | NRG Oncology/ NSABP B-47 menstrual history study | Prospective | Weekly AC–paclitaxel ± trastuzumab | No evidence that trastuzumab contributed to transient amenorrhea. |
| Ruddy *et al* (2021) [15] | 123 | CRA after adjuvant T-DM1 versus paclitaxel–trastuzumab (ATEMPT trial) | Prospective | Paclitaxel + trastuzumab versus trastuzumab emtansine (T-DM1) | Amenorrhea rates in women treated with TH or T-DM1 were lower than expected for standard cytotoxic regimens. |
| Lambertini *et al* (2019) [16] | 2,862 | Adjuvant Anti-HER2 Therapy, TRA, and Survival (ALTTO – BIG 2-06) | Retrospective | Trastuzumab, lapatinib, sequential or combined | Similar amenorrhea rates across all arms ($p = 0.64$). |
| Jueckstock *et al* (2016) [17] | 30 | Expression of Activin During and After Chemotherapy (SUCCESS A study) | Prospective | FEC → Docetaxel versus FEC → Gemcitabine–Docetaxel | Trastuzumab correlated with a significant decrease in activin A concentration. |
| Ruddy *et al* (2021) [18] | 277 | AMH as a biomarker for chemotherapy-induced amenorrhea (NRG Oncology/ NSABP B-47) | Prospective | Weekly AC–Paclitaxel ± trastuzumab | Trastuzumab did not increase amenorrhea rates. |
| Abusief *et al* (2010) [19] | 431 | Effects of paclitaxel, dose density, and trastuzumab on TRA | Retrospective | Dose-dense AC–Paclitaxel ± trastuzumab | Amenorrhea rates did not differ significantly across regimens. |
| Lambertini *et al* (2019) [20] | N/A | Oncofertility counselling in premenopausal women with HER2-positive breast cancer | Descriptive | — | Provided information on fertility preservation in HER2-positive patients. |

*Continued*

**Table 1. Clinical trials evaluating gonadotoxicity in patients with HER2-positive breast cancer.** *Continued*

| | | | | | |
|---|---|---|---|---|---|
| Lambertini *et al* [16, 20] | 38 | Adverse reproductive health outcomes in young women with breast cancer (prospective cohort) | Prospective | Chemotherapy ± trastuzumab | Higher AMH levels in women treated with trastuzumab, suggesting reduced gonadotoxicity. |
| Morarji *et al* (2017) [22] | 176 | Ovarian function after chemotherapy in young breast cancer survivors | Prospective | Various regimens ± trastuzumab | Trastuzumab associated with higher AMH levels in survivors; AMH similar to controls. |
| Poorvu *et al* (2021) [23] | 789 | TRA in a modern prospective cohort of young women with breast cancer | Prospective | T/Carbo/Trastuzumab ± pertuzumab; TC ± trastuzumab/pertuzumab; ACT ± trastuzumab/ pertuzumab; AC alone; Paclitaxel/trastuzumab | TRA rates were similar across regimens, but lower in paclitaxel–trastuzumab combinations. |

**Table legend:** Summary of clinical and translational studies assessing trastuzumab-related gonadotoxicity, amenorrhea and ovarian reserve markers in HER2-positive breast cancer patients [13].
**Abbreviations:** CRA, chemotherapy-related amenorrhea; AC, doxorubicin–cyclophosphamide; FEC, fluorouracil–epirubicin–cyclophosphamide; AMH, anti-Müllerian hormone; TH, paclitaxel–trastuzumab; T-DM1, trastuzumab emtansine; TRA, treatment-related amenorrhea; ACT, doxorubicin–cyclophosphamide–taxane; TC, docetaxel–cyclophosphamide; CMF, cyclophosphamide–methotrexate–fluorouracil; CEF, cyclophosphamide–epirubicin–fluorouracil. NA, not available



## Discussion

### *Impact on amenorrhea*

Treatment-induced amenorrhea can be influenced by several factors, including the patient's age, duration of treatment and dose administered [6]. The literature suggests that the impact of trastuzumab on amenorrhea can be modified by the presence of other chemotherapeutic agents and the intensity of treatment itself [15, 16].

The article describing amenorrhea after chemotherapy treatment offered in the 'APT trial' [13] reports that the administration of paclitaxel and trastuzumab is associated with a significant rate of chemotherapy-induced amenorrhea. This is corroborated by other studies indicating that the combination of treatments may have additive effects on ovarian function [5, 15].

Comparison with other chemotherapy regimens, such as trastuzumab administration with emtansine (T-DM1), has also been shown to have an impact on amenorrhea, but with variability in results [15]. Comparison between treatments reveals that the presence of trastuzumab may worsen the incidence of amenorrhea, especially in regimens that are already known to be highly gonadotoxic [13].

Although trastuzumab may contribute to amenorrhea, its impact on patient survival should also be considered. A real-life Brazilian study described the effectiveness of adjuvant trastuzumab in women with HER2-positive early breast cancer treated by the Brazilian public health system. The 8.7-year survival rate was 85.9%, while the disease-free survival rate over the same period was 62.8%. These rates are similar to those observed in international clinical trials [24].

A meta-analysis of individual patient data from randomised trials evaluating chemotherapy plus trastuzumab versus trastuzumab alone, which included 13,864 patients enrolled between February 2000 and December 2005, demonstrated that adding trastuzumab to chemotherapy

for early-stage HER2-positive breast cancer reduces breast cancer recurrence and mortality by one-third, with proportional reductions valid regardless of recorded patient and tumour characteristics [25].

Furthermore, studies show that treatment-induced amenorrhea is not necessarily associated with a worse long-term prognosis, despite having important implications for quality of life and fertility [3, 14].

### *Prospects for fertility preservation*

Fertility preservation is a major concern for young breast cancer patients treated with trastuzumab. Strategies such as egg or embryo cryopreservation are frequently discussed and recommended to minimise the impact of treatment on fertility. Awareness and provision of preservation options are crucial for comprehensive patient management [2, 4].

### *Protective effect or reduction of amenorrhea due to trastuzumab*

The Atempt trial [15] compared amenorrhea induced by trastuzumab treatment with emtansine (T-DM1) with the combination of paclitaxel and trastuzumab. The results suggest that T-DM1, an antibody-drug conjugate containing trastuzumab, may have a different amenorrhea profile compared to trastuzumab in combination with paclitaxel. This suggests that the form of trastuzumab used may impact ovarian function differently, possibly indicating a less detrimental effect in terms of amenorrhea.

Another study by the same author [18] explores the use of AMH as a biomarker to predict chemotherapy-induced amenorrhea. Although it does not focus exclusively on trastuzumab, it may help understand how different agents, including trastuzumab, affect ovarian function and amenorrhea. The relationship between AMH and treatment may imply variations in the effects on ovarian function depending on the treatment regimen.

Richani and Gilchrist [12] published an article in 2018 that discusses the role of the epidermal growth factor network in oocyte maturation and competence. While it does not directly focus on trastuzumab, it provides insight into how modulation of the growth factor network can affect ovarian function. Understanding this network can help interpret the potential impact of treatments like trastuzumab on ovarian function [12].

### *Limitations*

This review has some limitations that should be acknowledged. First, the number of studies specifically evaluating the isolated effect of trastuzumab on ovarian reserve is limited. Second, there is marked heterogeneity among the included studies regarding study designs, chemotherapy regimens used in combination with trastuzumab and the definitions of clinical outcomes such as amenorrhea. Such heterogeneity, combined with the lack of a standardised risk-of-bias assessment and the absence of prospective protocol registration, limits the ability to draw definitive conclusions or perform a quantitative synthesis (meta-analysis).

## Conclusion

Of the 11 articles analysed, four show that trastuzumab has no influence on the incidence of amenorrhea. One study suggests an increase in amenorrhea when trastuzumab is combined with chemotherapy, while four others observe a decrease in amenorrhea, accompanied by the preservation of AMH levels. These findings suggest possible ovarian protection conferred by trastuzumab. Finally, two articles do not address this issue within their original research scope.

Given the lack of consensus in the literature, premenopausal women diagnosed with HER2-positive breast cancer face a gap in the available evidence to guide them regarding potential gonadotoxicity. Given this lack of substantial information, we suggest conducting a prospective

study to evaluate the impact of including trastuzumab in chemotherapy. This study should compare the amenorrhea rate of the same chemotherapy regimen, both with and without the addition of trastuzumab, to provide more robust data on treatment-related amenorrhea.

In light of the above, the need to provide all premenopausal patients with comprehensive counseling on oncofertility before starting any cancer treatment is highlighted. This extremely important discussion not only represents an essential step in empowering patients to make fully informed choices about the proposed therapy and its potential long-term implications, but also promotes reflection on the relevance and interest of adopting available strategies to preserve ovarian function.

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## Conflicts of interest

Nothing to declare.

## Funding

Nothing to declare.

## Ethical approval

Not applicable. This systematic review did not involve human participants or animal experiments.

## Author contributions

All authors contributed substantially to the conception and/or planning of the study; in obtaining, analysing and/or interpreting the data; in writing and/or critically reviewing it; and approved the final version to be published.

## Artificial intelligence

Artificial intelligence tools (OpenAI GPT-5) were used solely to assist with language editing, formatting and compliance with journal submission requirements. The authors reviewed and approved all content.

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