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Efficacy of goserelin in ovarian function suppression and preservation for pre- and perimenopausal breast cancer patients: a systematic review

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Abstract

Background: Over the past few decades, the gonadotropin-releasing hormone agonist goserelin has been evaluated in ovarian function suppression (OFS) with adjuvant endocrine therapy and ovarian function preservation (OFP) during chemotherapy.

Objective: The goal of this systematic literature review was to assess the efficacy of goserelin in OFS and OFP in combination with endocrine therapies and chemotherapy, respectively, in pre- and perimenopausal women with early-stage breast cancer.

Design: This study is a systematic review.

Data sources and methods: The literature search was conducted using PubMed. Prospective clinical studies evaluating the efficacy of goserelin in OFS or OFP in pre- or perimenopausal breast cancer were identified by four reviewers working in teams of two.

Results: Twenty-nine studies were included in this systematic review. The addition of goserelin as OFS to adjuvant endocrine therapy generally resulted in significant benefits in disease-free survival. Studies have shown better OFP results among women 40 years or younger compared with older patients. Chemotherapy in association with goserelin for OFP resulted in a higher recovery rate of menses within 6–24 months, a shorter time for menstrual recovery, and significantly higher pregnancy rates when compared with cytotoxic therapy without goserelin. Hormonal recovery with higher anti-Müllerian hormone and estradiol levels, and lower follicle-stimulating hormone and luteinizing hormone levels occurred more frequently among women who received goserelin during chemotherapy as compared with those receiving cytotoxic therapy alone. The benefits of goserelin in OFP were more substantial among women 40 years or younger than in older patients.

Conclusion: The findings of this systematic review highlight the benefits of adding goserelin to endocrine therapies for OFS and chemotherapy for OFP in early-stage breast cancer. Additionally, scientific data supporting OFS (including goserelin) in combination with newer agents such as cyclin-dependent kinase 4 and 6 inhibitors and bone-modifying agents are emerging.

Keywords: bone-modifying agents, breast cancer, CDK4/6 inhibitor, early-stage breast cancer, efficacy, GnRH agonist, goserelin, oncofertility, ovarian function suppression, premenopausal

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Introduction

Goserelin, a gonadotropin-releasing hormone (GnRH) agonist, was approved by the United States Food and Drug Administration in 1995 for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.[1,2] Since then, goserelin has been approved in over 60 countries worldwide for breast cancer as a subcutaneous injection of 3.6 mg every 4 weeks (Q4W) or 10.8 mg every 12 weeks (Q12W).[3] Chronic administration of goserelin inhibits pituitary gonadotropin secretion and suppresses serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, resulting in a decrease in serum estradiol (E_2) levels consistent with the postmenopausal state in women.[2] This is expected to result in a reduction in the size and function of the ovaries, a decrease in the size of the uterus and mammary glands, and regression of sex hormone-responsive tumors.[2]

Goserelin has been well studied for ovarian function suppression (OFS) as part of endocrine therapy and new trials continue to incorporate its use in combination with modern breast cancer therapies.[4,5] Early data evaluating goserelin monotherapy versus oophorectomy demonstrated similar outcomes in women with advanced breast cancer.[6–8] Furthermore, a previous systematic review and meta-analysis showed that goserelin can be added to endocrine therapy for OFS in the advanced/metastatic setting, leading to improvements in progression-free survival and overall survival (OS).[4,5]

In patients with early-stage (defined as non-metastatic) breast cancer receiving chemotherapy, the use of goserelin as ovarian function preservation (OFP) has significantly reduced the incidence of treatment-induced premature ovarian failure in women receiving chemotherapy.[9,10] Furthermore, significantly more patients were able to achieve a pregnancy after completing GnRH agonist therapy than in the chemotherapy alone group.[9]

The goal of this systematic literature review is to summarize the efficacy of goserelin as OFS as adjuvant endocrine therapy and OFP during (neo)adjuvant chemotherapy in pre- and perimenopausal women diagnosed with early-stage breast cancer.

Methods

This systematic review was performed according to the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[11] The PRISMA checklist for the systematic review and the corresponding abstract are available for reference in Supplemental Table S1(A) and (B), respectively.

Search strategy

A PubMed literature search was conducted on February 13, 2024, using the terms (Goserelin OR GnRH OR LHRH) AND (breast cancer OR breast neoplasm) with no filters applied. An updated search was conducted on June 4, 2024, prior to the preparation of this manuscript. Results were exported to EndNote for proper formatting and then exported into a Microsoft Excel file used by the authors for the screening process.

Selection criteria

Four reviewers worked in teams of two and divided the search results to screen titles and abstracts using predefined exclusion criteria. Authors S.S. and N.O. reviewed half of the results while author R.M. and reviewer J.U., reviewed the other half of the results. Initial pre-defined inclusion criteria consisted of the following parameters: published in English, full-length manuscripts (e.g., posters/abstracts were excluded), primary data source (e.g., review articles and meta-analyses were excluded after cross-checking their reference lists for potential studies to be included), inclusion of $\geqslant$10 patients, clinical studies in pre- or perimenopausal women being treated for breast cancer with goserelin as a component of the therapeutic regimen. If a publication did not meet the above criteria, it was categorized as "not relevant."

After applying the initial exclusion criteria, it was determined that the number of publications identified for inclusion was excessive for the purposes of a systematic literature review ($n=214$, Figure 1). At this point, expert clinician authors M.L., N.C., D.B., and H.K. proposed additional exclusion and inclusion criteria to identify the most clinically relevant studies. Author S.S. reviewed the 214 studies against the additional inclusion/exclusion criteria, with review by authors J.C. and R.M.

Other exclusion criteria were retrospective studies, trials in advanced/metastatic breast cancer patients, and all studies in which tamoxifen and goserelin were administered concurrently with

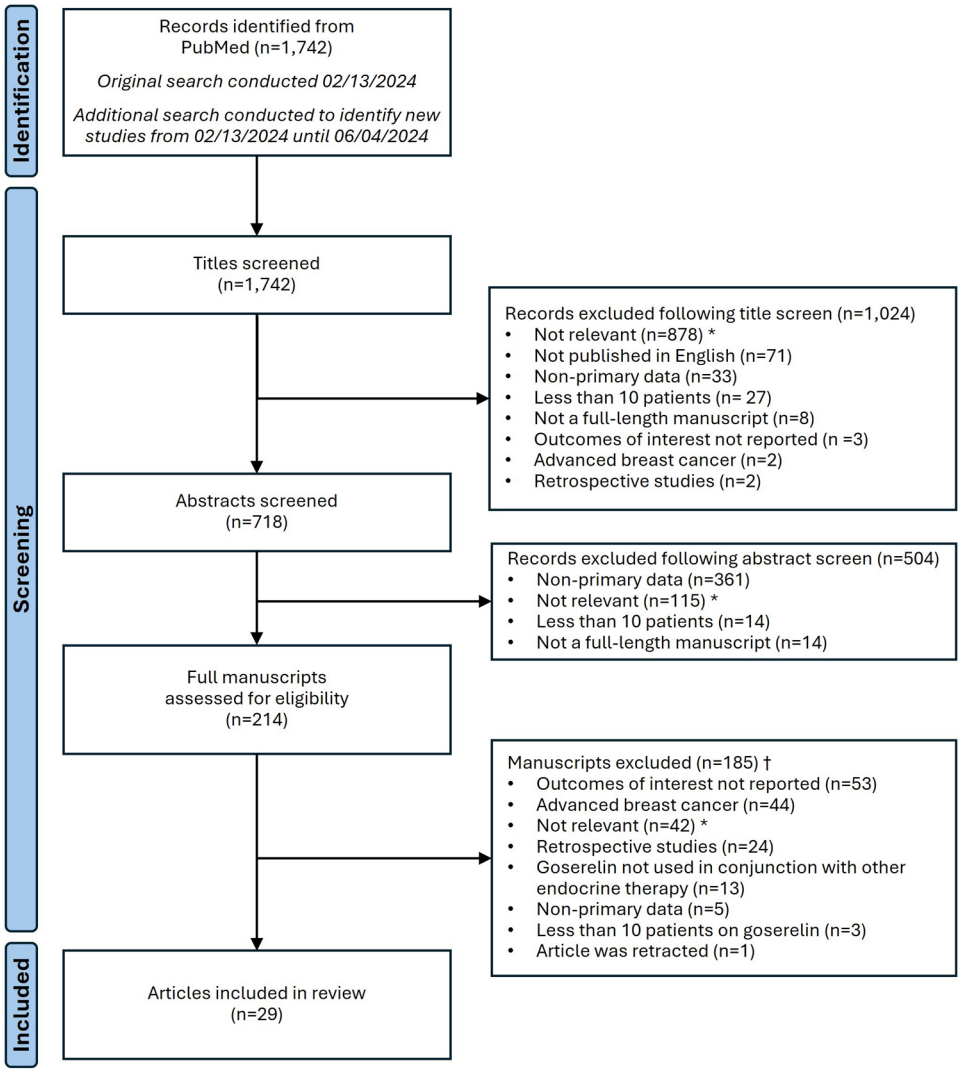

Figure 1. PRISMA flowchart of the systematic literature search.
*Not relevant defined as studies that were not conducted in premenopausal women with breast cancer using goserelin.
†Due to the high volume of studies retrieved, additional exclusion criteria were developed at this point to identify the most rigorous data and clinically relevant outcomes.
OFP, ovarian function preservation; OFS, ovarian function suppression; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

chemotherapy. Additional inclusion criteria included the use of goserelin in combination with endocrine therapies or with chemotherapy. Since the first approval of goserelin for breast cancer in 1995,[1,2] it is now well established that GnRH agonists should not be given as monotherapy, but rather in combination with endocrine therapy as OFS or with chemotherapy as OFP. Therefore, this criterion was included to evaluate only studies that reflect current clinical practice. Furthermore, as the addition of goserelin is already established as a standard of care in the metastatic setting, the focus of this review was on patients with early-stage breast cancer.[12] For studies reporting efficacy, disease-free survival (DFS) and/or OS were deemed to be the most relevant endpoints to assess efficacy among patients with early-stage breast cancer. In general, DFS is defined as the length of time from randomization to any evidence of disease recurrence (e.g., recurrence, distant disease, secondary malignancy, death).[13–15] DFS is often a preferred surrogate endpoint in early-stage breast cancer trials as it requires fewer patients and shorter follow-up periods than OS.[13–16] OS is defined as the length of time from randomization to death from

any cause.[13–15] OS remains the gold standard to assess the efficacy of a treatment in breast cancer clinical trials but requires a large patient population and a longer follow-up period for events to mature.[13–16] In addition, when DFS or OS were not included as an efficacy endpoint, studies reporting other survival outcomes such as event-free survival (EFS), relapse-free survival (RFS), or time to recurrence/recurrence-free survival were included. Studies evaluating goserelin as a therapy for OFP were included if they reported at least one of the following outcomes: recovery of menses, pregnancy, anti-Müllerian hormone (AMH), E_2, FSH, and/or LH levels. These outcomes of interest were determined by the expert clinician authors to be the most relevant and informative.

Data collection

For each of the included studies, data was extracted to populate parameters set forth in Tables 1–3 including author, year, study design, treatment arms, patient population (ER+/PR+/HER2+ status, stage 1 or 2, age), survival outcomes (e.g., DFS, OS, EFS, RFS, recurrence-free survival), and OFP outcomes (recovery of menses, pregnancy, AMH, E_2, FSH, and/or LH levels).

Results

Search results

A PubMed literature search conducted on February 13, 2024, yielded 1729 citations, with an update conducted on June 4, 2024, to identify any additional publications shortly before initiating manuscript preparation, adding 13 additional citations for a total of 1742 records (Figure 1). Among them, 718 titles passed title screening and proceeded to abstract review. Following abstract review, 214 articles proceeded to full paper review, and 29 articles were included in this review. Out of these 29 articles, 16 reported DFS and/or OS efficacy data as the primary endpoint for OFS for goserelin with or without endocrine therapies (Table 1)[17–32] and 9 reported OFP data for goserelin in combination with chemotherapy (Table 2).[33–41] In addition, 1 article reported efficacy data for goserelin plus an aromatase inhibitor (AI) with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor,[42] and 3 articles reported efficacy data for goserelin plus zoledronic acid (Table 3).[43–45]

OFS as adjuvant endocrine therapy

DFS and OS with goserelin combination therapy.

Among the 16 publications reporting data from 12 randomized studies evaluating DFS, OS, or other survival outcomes in OFS, the initial studies comparing goserelin ± tamoxifen versus chemotherapy in the adjuvant setting were published in 2000 and 2002 (Table 1(a) and Figure 2), and in the neoadjuvant setting in 2021 (Table 1(b) and Figure 2).[17–19] The studies assessing goserelin ± tamoxifen ± chemotherapy were published between 2006 and 2022 (Table 1(c) and Figure 2).[20–24] In 2005, studies on the use of goserelin after completion of chemotherapy began to be published. This topic continued to be investigated through the next two decades with six studies published along with a long-term follow-up study evaluating goserelin ± tamoxifen (Table 1(d) and (e) and Figure 2).[25–28,30–32]

In the adjuvant chemotherapy setting, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 5, which included 1034 premenopausal women, showed no difference in the 5-year OS between goserelin plus tamoxifen and chemotherapy.[18] However, the 5-year recurrence-free survival data from ABCSG Trial 5 was significantly better with goserelin plus tamoxifen than with chemotherapy (83% vs 79%; $p = 0.037$; Table 1(a)).[18] A smaller study by Boccardo et al showed comparable 6-year OS and DFS between OFS (either surgical oophorectomy/ovarian irradiation or goserelin) plus tamoxifen versus adjuvant chemotherapy in 244 pre- or perimenopausal women with ER+ breast cancer (Table 1(a)).[17] In the neoadjuvant setting, no significant difference was observed between goserelin plus tamoxifen versus chemotherapy for 5-year DFS and OS in the study of chemotherapy versus endocrine therapy in premenopausal patients with hormone receptor positive, HER2-negative, lymph node-positive breast cancer (NEST; Table 1(b)).[19]

The efficacy of goserelin ± tamoxifen and/or chemotherapy was first investigated in the ZIPP trial, with 5-year data reported in 2006 and 12-year data reported in 2009. In the 5-year ZIPP analysis, significantly better OS (86% vs 83%; $p = 0.038$) and EFS (73% vs 68%; $p = 0.002$) were observed with goserelin than without goserelin (Table 1(c)).[20] In the 12-year ZIPP analysis, this significant difference was maintained for both OS (77% vs 72%; $p = 0.013$) and EFS (60% vs 55%; $p = 0.001$) with goserelin versus without goserelin (Table 1(c)).[21] In another ZIPP trial publication,

Table 1. Ovarian function suppression in pre- and perimenopausal women with early-stage breast cancer on goserelin combination therapy.

Author, year	Study design; treatment arms	Patient population	Disease-free survival	OS	Other survival outcomes
(a) Goserelin + tamoxifen versus chemotherapy (adjuvant)					
Boccardo 2000[17]	Prospective, multicenter RCT Goserelin 3.6 mg QM × 2 y + tamoxifen 30 mg QD × 5 y (n = 87) Surgical oophorectomy/ovarian irradiation + tamoxifen 30 mg QD × 5 y (n = 37) Chemotherapy × 6 cycles (n = 120)	Pre- or perimenopausal ER+ women ⩾35 y with early-stage breast cancer *ER+:* 100% *Grade 1 or 2:* 73% *Age*, median (range): 46 y (28–57)	No difference between OFS (goserelin or oophorectomy/ovarian irradiation) + tamoxifen vs chemotherapy *Median 76 months (6 y, 1°):* 67% goserelin + tamoxifen 62% oophorectomy/ovarian irradiation + tamoxifen	No difference between OFS (goserelin or oophorectomy/ovarian irradiation) + tamoxifen vs chemotherapy *Median 76 months (6 y, 1°):* 86% goserelin + tamoxifen 84% oophorectomy/ovarian irradiation + tamoxifen	
Jakesz 2002[18] ABCSG Trial 5	Prospective, multicenter RCT Goserelin 3.6 mg Q4W × 3 y + tamoxifen 20 mg QD × 5 y (n = 511) Chemotherapy × 6 cycles (n = 523)	Premenopausal women with stage 1–2, HR+ (ER+ and/or PR+) breast cancer *ER+/strongly ER+:* 93% *PR+/strongly PR+:* 89% *Grade 1 or 2:* 97% *Age <35 y:* 7%		*5-y (1°):* 92% goserelin + tamoxifen 90% chemotherapy p = 0.190	*5-y RFS (2°):* 83% goserelin + tamoxifen 79% chemotherapy RR (95% CI): 1.4 (1.06–1.87) p = 0.037
(b) Goserelin + tamoxifen versus chemotherapy (neoadjuvant)					
Gwark 2021[19] NEST Trial	Prospective, multicenter, phase III RCT Goserelin 3.6 mg Q4W + tamoxifen 20 mg QD × 24 weeks prior to surgery (n = 83) Chemotherapy × 24 weeks prior to surgery (n = 87)	Premenopausal women with ER+, HER2–, LN+ breast cancer *ER+:* 100% *PR+:* 88% *HER2+:* 0% *Stage 1 or 2:* 82% *Age*, median (range): 42 y (27–54)	*5-y (2°):* 85% goserelin + tamoxifen 77% chemotherapy; p = 0.166	*5-y (2°):* 95% goserelin + tamoxifen 98% chemotherapy; p = 0.304	
(c) Goserelin ± tamoxifen ± chemotherapy					
Baum 2006[20] Hackshaw 2009[21] ZIPP trial (CRUK BCTG, Stockholm, SE Sweden, and GIVIO)	Multicountry, prospective RCT; Goserelin 3.6 mg Q4W × 2 y ± tamoxifen 20 or 40 mg QD × 2 y ± chemotherapy (n = 1354 in Baum 2006; n = 1351 in Hackshaw 2009) No goserelin (tamoxifen 20 or 40 mg QD × 2 y and/or chemotherapy, n = 1356 in Baum 2006; n = 1355 in Hackshaw 2009)	Premenopausal women or women <50 with early-stage breast cancer *ER+:* 51% *Stage 1 or 2:* 100% *Age*, median: 44 y; *Age ⩽39 y:* 22%		*5-y (1°):* 86% goserelin 83% no goserelin HR (95% CI): 0.81 (0.67–0.99); p = 0.038 *12-y (1°):* 77% goserelin 72% no goserelin HR (95% CI): 0.83 (0.71–0.96); p = 0.013	*5-y EFS (1°):* 73% goserelin 68% no goserelin HR (95% CI): 0.80 (0.69–0.92); p = 0.002 *12-y EFS (1°):* 60% goserelin 55% no goserelin; HR (95% CI): 0.82 (0.73–0.92); p = 0.001 *12-y recurrence-free survival (2°):* 70% goserelin 65% no goserelin HR (95% CI): 0.81 (0.71–0.92); p = 0.001 *12-y breast cancer survival (2°):* 82% goserelin 79% no goserelin HR (95% CI): 0.82 (0.70–0.96); p = 0.03

(Continued)

Table 1. (Continued)

Author, year	Study design; treatment arms	Patient population	Disease-free survival	OS	Other survival outcomes
Sverrisdottir 2011[22] ZIPP trial (Stockholm STO-5)	Prospective RCT Goserelin 3.6 mg Q4W × 2 y (n = 231) Tamoxifen 40 mg QD × 2 y (n = 231) Goserelin 3.6 mg Q4W + tamoxifen 40 mg QD × 2 y (n = 231) No endocrine therapy (control) (n = 234)	Premenopausal women with early-stage breast cancer *ER+:* 64% *Age*, mean: 45.6 y			*12-y EFS (1°):* 58% goserelin 56% tamoxifen 53% goserelin + tamoxifen 45% control *12-y recurrence-free survival (2°):* ~56% goserelin ~50% no goserelin HR (95% CI): 0.84 (0.68–0.92); p = 0.001
Zhong 2019[23]	Prospective RCT Goserelin 3.6 mg Q4W[a] + chemotherapy + tamoxifen for HR+ patients (n = 51) Chemotherapy + tamoxifen for HR+ patients (n = 45)	Premenopausal women ⩽45 y with stage 1–3A breast cancer *ER+:* 69% *HER2+:* 30% (trastuzumab treatment permitted) *Stage 1 or 2:* 95% *Age*, median: 39 y; *Age<40 y:* 55%	*1-y (2°):* 94% goserelin + chemotherapy 97% chemotherapy; p = 0.804	*1-y (2°):* 100% goserelin + chemotherapy 100% chemotherapy; p = 0.298	
Johansson 2022[24] ZIPP trial (Stockholm STO-5) subanalysis	Prospective RCT Goserelin 3.6 mg Q4W × 2 y ± chemotherapy (n = 155) Tamoxifen 40 mg QD × 2 y ± chemotherapy (n = 135) Goserelin 3.6 mg Q4W + tamoxifen 40 mg QD × 2 y ± chemotherapy (n = 149) No endocrine therapy (control) ± chemotherapy (n = 145)	Premenopausal women with breast cancer *ER+: 100%* *PR+:* 91% *HER2+:* 12% *Stage 1 or 2:* 76% *Age*, median (range): 47 y (26–55); *Age <45y:* 29%			*20-y survival by DRFI (1°):* 72% goserelin 66% tamoxifen 67% goserelin + tamoxifen 60% control HR (95% CI): 0.49 (0.32–0.75; p = 0.026) vs goserelin arm
(d) Chemotherapy → goserelin + tamoxifen					
De Placido 2005[25] MAM1 Trial	Prospective RCT Chemotherapy × 6–10 cycles → goserelin 3.6 mg Q4W × 2 y + tamoxifen 20 mg QD × 2 y (n = 233) Chemotherapy × 6–10 cycles (n = 233)	Premenopausal women with LN+ early-stage breast cancer *ER+:* 38% *PR+:* 33% *Grade 1 or 2:* 25% *Age*, median (range): 44 y (20–52)	*5-y (1°):* 64% chemotherapy → goserelin + tamoxifen 53% chemotherapy; p = 0.044	*5-y (2°):* 82% chemotherapy → goserelin + tamoxifen 80% chemotherapy; HR (95% CI): 0.84 (0.54–1.32); p = 0.48	
Davidson 2005[26] INT 0101 (E5188) Trial	Prospective, phase III RCT Chemotherapy × 6 cycles → goserelin 3.6 mg Q4W × 5 y + tamoxifen 10 mg BID × 5 y (n = 507) Chemotherapy × 6 cycles → goserelin 3.6 mg Q4W × 5 y (n = 502) Chemotherapy × 6 cycles (n = 494)	Premenopausal women with ER+ and/or PR+, LN+ breast cancer *ER+:* 87% *PR+:* 89% *Nodes:* 59% with 1–3 *Age<40 y:* 29%	*9-y (1°):* 68% chemotherapy → goserelin + tamoxifen 60% chemotherapy → goserelin, HR (95% CI): 0.74 (0.60–0.91); p < 0.01 vs chemotherapy → goserelin + tamoxifen 57% chemotherapy, HR (95% CI): 0.93 (0.76–1.12); p = 0.22 vs chemotherapy → goserelin	*9-y (1°):* 76% chemotherapy → goserelin + tamoxifen 73% chemotherapy → goserelin, HR (95% CI): 0.91 (0.71–1.15); p = 0.21 vs chemotherapy → goserelin + tamoxifen 70% chemotherapy, HR (95% CI): 0.88 (0.70–1.11); p = 0.14 vs chemotherapy → goserelin	

(Continued)

Table 1. (Continued)

Author, year	Study design; treatment arms	Patient population	Disease-free survival	OS	Other survival outcomes
Uslu 2014[27]	Prospective, RCT Chemotherapy → goserelin 3.6 mg QM ×2 y + tamoxifen 20 mg QD × 5 y (n = 50) Chemotherapy → tamoxifen 20 mg QD × 5 y (n = 51)	Premenopausal women with stage 2–3C, LN+ and HR+ (ER+ and/or PR+) breast cancer *ER+:* 45% *PR+:* 46% *Stage 2:* 34% *Age, mean*: 47 y	*Mean 57 months (5 y, 1°):* 86% goserelin + tamoxifen 76% tamoxifen; HR = 0.55; p = 0.23 *Mean (SD):* 49.9 (4.2) mo goserelin + tamoxifen 43.0 (3.6) mo tamoxifen; p = 0.13	*Mean 57 months (5 y; 2°):* 93% goserelin + tamoxifen 83% tamoxifen; HR (95% CI): 0.93 (0.24–1.41) *Mean (SD):* 53.1 (4.2) mo goserelin + tamoxifen 51.1 (3.8) mo tamoxifen; p = 0.5	
Kim 2020[28] Baek 2023[29] ASTRRA Trial	Prospective, open-label, multicenter, phase III RCT Chemotherapy → goserelin 3.6 mg Q4W × 2 y + tamoxifen 20 mg QD × 5 y (n = 635 for Kim, 2020; n = 610 for Baek, 2023) Chemotherapy → tamoxifen 20 mg QD × 5 y (n = 647 for Kim, 2020; n = 621 for Baek, 2023)	Premenopausal women ⩽45 y with ER+, stage 1–3 breast cancer *ER+:* 100% *HER2+:* 14% (HER2-targeted therapy permitted) *Grade 1 or 2:* 68% *Age*, median (range): 40 (24–45); *Age < 40y:* 42%	*5-y (1°):* 91% goserelin + tamoxifen 88% tamoxifen; HR (95% CI): 0.69 (0.48–0.97); p = 0.033 8 y (1°): 85% goserelin + tamoxifen 80% tamoxifen; HR (95% CI): 0.67 (0.51–0.87), p = 0.003 *8 y for age <* 35 y[b]: 78% goserelin + tamoxifen 73% tamoxifen; HR (95% CI): 0.74 (0.41–1.33) 8 y for age 35–39 y[b]: 81% goserelin + tamoxifen 83% tamoxifen; HR (95% CI): 0.99 (0.62–1.60) 8 y for age 40–45 y[b]: 89% goserelin + tamoxifen 80% tamoxifen; HR (95% CI): 0.50 (0.34–0.73)	*Median 63 months (5y; 2°):* 99% goserelin + tamoxifen 98% tamoxifen; HR (95% CI): 0.31 (0.10–0.94); p = 0.029 *8 y (2°):* 97% goserelin + tamoxifen 95% tamoxifen; HR (95% CI): 0.78 (0.49–1.25), p = 0.305	*8y RFI (2°):* 88% goserelin + tamoxifen 83% tamoxifen; HR (95% CI): 0.70 (0.52–0.93) *8y BCFI (2°):* 86% goserelin + tamoxifen 82% tamoxifen; HR (95% CI): 0.71 (0.54–0.94) *8y DMFS (2°):* 89% goserelin + tamoxifen 85% tamoxifen; HR (95% CI): 0.71 (0.52–0.96)
(e) Chemotherapy (→tamoxifen)→goserelin					
IBCSG 2003[30] Karlsson 2011[31] IBCSG Trial VIII	Multicenter RCT Chemotherapy × 6 cycles → goserelin 3.6 mg Q4W × 1.5 y (n = 357) Goserelin 3.6 mg Q4W × 2 y (n = 346) Chemotherapy × 6 cycles (n = 360)	Pre- and perimenopausal patients with breast cancer *ER+:* 81% *Grade 1 or 2:* 61% *Age < 40y:* 20%	*5-y (ER+ group):* 88% chemotherapy → goserelin 82% goserelin 84% chemotherapy *12-y (ER+ group):* 77% chemotherapy → goserelin 68% goserelin; HR (95% CI): 0.71 (0.51–0.98), p = 0.04 69% chemotherapy; HR (95% CI): 0.71 (0.52–0.99), p = 0.04	*5-y (ER+ group):* 97% chemotherapy → goserelin 97% goserelin 94% chemotherapy *12-y (ER+ group):* 90% chemotherapy → goserelin 87% goserelin 84% chemotherapy	

(Continued)

Table 1. (Continued)

Author, year	Study design; treatment arms	Patient population	Disease-free survival	OS	Other survival outcomes
Li 2019[32]	Prospective, open-label RCT Chemotherapy → tamoxifen (or toremifene) ×2–3 y → goserelin 3.6 mg Q4W × 2–3 y + anastrozole 1 mg QD × 2–3 y (n = 33) Chemotherapy → tamoxifen (or toremifene) × 5 y (n = 29)	Premenopausal women with HR+, early-stage breast cancer *ER+:* 89% *PR+:* 92% *HER2+:* 0% *Age*, median (range): 41 y (29–51)	*2-y (2°):* 80% goserelin 80% tamoxifen only p = 0.77 *Median 34 months (3-y):* 85% goserelin 90% tamoxifen only	*2-y (2°):* 100% goserelin 100% tamoxifen only	

[a]Started within 1 week of chemotherapy and continued to within 2 weeks of the final chemotherapy.
[b]At enrollment.
1°, primary endpoint; 2°, secondary endpoint; ABCSG, Austrian Breast and Colorectal cancer Study Group; ASTRRA, Addition of ovarian Suppression to Tamoxifen in young women with hormone-sensitive breast cancer who Remain premenopausal or Regain vaginal bleeding After chemotherapy; BCFI, breast cancer-free interval; BCTG, Breast Cancer Trials Group; BID, twice daily; CI, confidence interval; CRUK, Cancer Research United Kingdom; DFRI, distant recurrence-free interval; DMFS, distant metastasis-free survival; EFS, event-free survival; ER+, estrogen receptor positive; GIVIO, Gruppo Interdisciplinare Valutazione Interventi in Oncologia; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; IBCSG, International Breast Cancer Study Group; INT, Intergroup; LN, lymph node; NEST, Neoadjuvant study of chemotherapy versus Endocrine therapy in premenopausal patient with hormone responsive, HER2-negative, lymph node-positive breaST; OFS, ovarian function suppression; POEMS, Prevention of Early Menopause; PR+, progesterone receptor positive; Q4W, every 4 weeks; QD, once daily; QM, every month; RCT, randomized controlled trial; RFI, recurrence-free interval; RFS, relapse-free survival; RR, relative risk; SD, standard deviation; SE, South-East; STO-5, Stockholm trial 5; y, years; ZIPP, Zoladex In Pre-menopausal Patients.

Table 2. Ovarian function preservation in pre- and perimenopausal women with early-stage breast cancer on goserelin + chemotherapy.

Author, year	Study design; treatment arms	Patient population	Recovery rate of menses and pregnancy outcomes	E_2, FSH, LH, and AMH levels	Other endpoints
Del Mastro 2006[33]	Prospective, phase II study Goserelin 3.6 mg Q4W + chemotherapy (n = 29)	Premenopausal patients with stage 1–3 breast cancer *ER+ and/or PR+:* 86% *Grade 1 or 2:* 72% *Age: <40 y*: 59%	*1-y recovery:* 72% (21/29); 95% CI: 52–87 <40 y old: 94% (16/17) ≥40 y old: 42% (5/12) *Median time to recovery (range):* 5.5 (2.1–12) mo ≤35 y old: 2.7 mo (2.4–6.4) 36–38 y old: 6.1 mo (2.1–11.5) ≥39 y old: 7.9 mo (2.9–12.0)	*E_2 >20 pg/mL:* 65% (19/29) *Median E_2 level (range):* Recovery: 181 pg/mL (<20–766) Non-recovery: 23 pg/mL (<20–514), p = 0.03 *FSH ≤40 IU/L:* 83% (24/29) *Median FSH level (range):* Recovery: 6.09 IU/L (2.18–59.9) Non-recovery: 19.20 IU/L (9.16–32.3), p = 0.02	
Sverrisdottir 2009[34] ZIPP Trial ovarian function sub-study	Prospective RCT[a] Goserelin 3.6 mg Q4W ×2 y + chemotherapy (n = 63) Chemotherapy (n = 63)	Perimenopausal women with early-stage breast cancer *ER+:* 70% *PR+:* 66% *Age*, median (range): 45 y (29–55)	*6-mo recovery:* 33% goserelin 6% chemotherapy *1-y recovery:* 36% goserelin 10% chemotherapy	Not reported	
Gerber 2011[35] GBG-37 ZORO Study	Prospective, open-label, multicenter, phase II RCT Goserelin 3.6 mg Q4W + chemotherapy × 6–8 cycles (n = 30) Chemotherapy × 6–8 cycles (n = 30)	Premenopausal patients ≤45 y with ER–, PR– breast cancer *ER+:* 0% *PR+:* 0% *Age*, median (range): 37 y (26–47)	*6-mo recovery (95% CI):* 70% (54–86) goserelin + chemotherapy 57% (39–74) chemotherapy; difference: 13% (11–37); p = 0.142 *1-y recovery:* 83% goserelin + chemotherapy 80% chemotherapy *1.5 y recovery:* 90% goserelin + chemotherapy 87% chemotherapy *2-y recovery:* 93% goserelin + chemotherapy 93% chemotherapy *Overall (2-y) recovery:* 93% goserelin + chemotherapy 97% chemotherapy *Median time to recovery (95% CI):* 6.1 mo (5.3–6.8) goserelin + chemotherapy 6.8 mo (5.2–8.4) chemotherapy; p = 0.304 *Pregnancy:* 3% (1/30) goserelin + chemotherapy 3% (1/30; abortion) chemotherapy	*E_2 levels (6–24 mo):* 100–300 pmol/L goserelin + chemotherapy <100 pmol/L chemotherapy *FSH levels (6–24 mo):* <20 IU/L goserelin + chemotherapy 60–90 IU/L chemotherapy *LH levels (6–24 mo):* <15 IU/L goserelin + chemotherapy 30–50 IU/L chemotherapy; p = 0.015 at 12 mo *AMH levels > 0.2 mcg/L:* 50% (4/8) goserelin + chemotherapy 33% (3/9) chemotherapy	

(Continued)

Table 2. (Continued)

Author, year	Study design; treatment arms	Patient population	Recovery rate of menses and pregnancy outcomes	E_2, FSH, LH, and AMH levels	Other endpoints
Wong 2013[36]	Prospective study Goserelin 3.6 mg Q4W × 2 y[b] + chemotherapy → tamoxifen × 5 y for ER+ (n = 125)	Premenopausal women ⩽45 y with early-stage breast cancer *ER+:* 69% *Age*, median (range): 35 y (20–45); *Age <40 y*: 86% *Adjuvant:* 67% *Neoadjuvant:* 33%	*3-mo recovery:* 21% *6-mo recovery:* 54% *1-y recovery:* 82% *1.5-y recovery:* 94% *2-y recovery:* 95% *3-y recovery:* 99% *Overall recovery:* 89% in ⩽40 y old 56% in ⩾41 y old *Pregnancy:* 42 pregnancies 30 births (24%) 5 miscarriages, 3 voluntary terminations, 1 ectopic pregnancy, 3 pending deliveries *Median time to achieve pregnancy (range):* 40 mo (12–93)	Not reported	
Moore 2015[37] Moore 2019[38] POEMS/S0230 Study	Prospective, phase III RCT Goserelin 3.6 mg Q4W[b] + chemotherapy × 3–8 cycles (n = 105) Chemotherapy × 3–8 cycles (n = 113)	Premenopausal women with stage 1–3A, ER–, PR– breast cancer *ER+:* 0% *PR+:* 0% *HER2+:* 15% (trastuzumab treatment permitted) *Stage 1 or 2:* 74% *Age'*, median (range): 38 (25–50); *Age <40 y*: 63%	*2-y ovarian failure*[c]: 8% (5/66) goserelin + chemotherapy 22% (15/69) chemotherapy; OR (95% CI): 0.30 (0.09–0.97); p = 0.02 *1-y ovarian dysfunction*[d]: 23% (18/78) goserelin + chemotherapy 37% (28/75) chemotherapy *2-y ovarian dysfunction:* 14% (9/63 patients) goserelin + chemotherapy 33% (22/67) chemotherapy; OR (95% CI): 0.35 (0.13–0.93); p = 0.03 *2-y pregnancies:* 21% (22/105) goserelin + chemotherapy 11% (12/113) chemotherapy; OR (95% CI): 2.45 (1.09–5.51); p = 0.03 *2-y births:* 17% (18/105) goserelin + chemotherapy 11% (12/113) chemotherapy; p = 0.05 *5-y pregnancies (95% CI):* 23% (15–32) goserelin + chemotherapy 12% (6.8–19.2) chemotherapy; OR (95% CI): 2.34 (1.07–5.11); p = 0.03	Not reported	*4-y DFS:* 89% goserelin + chemotherapy 78% chemotherapy; HR (95% CI): 0.49 (0.24–0.97); p = 0.04 *5-y DFS:* 88% goserelin + chemotherapy 79% chemotherapy; HR (95% CI): 0.55 (0.27–1.10); p = 0.09 *4-y OS:* 92% goserelin + chemotherapy 82% chemotherapy; HR (95% CI): 0.43 (0.18–1.00); p = 0.05 *5-y OS:* 92% goserelin + chemotherapy 83% chemotherapy; HR (95% CI): 0.45 (0.19–1.04); p = 0.06

(Continued)

Table 2. (Continued)

Author, year	Study design; treatment arms	Patient population	Recovery rate of menses and pregnancy outcomes	E_2, FSH, LH, and AMH levels	Other endpoints
Leonard 2017[39] OPTION Trial	Prospective RCT Goserelin 3.6 mg Q3–4W[e] + chemotherapy × 6–8 cycles (n = 103) Chemotherapy × 6–8 cycles (n = 118)	Premenopausal women with stage 1–3B breast cancer *ER+:* 43% *Age:* 59% ⩽40 y *Age*, median (range): 38 y (25–51)	*1- to 2-y Recovery:* 78% goserelin + chemotherapy 90% in ⩽40 y old 62% chemotherapy (p = 0.015) 75% in ⩽40 y old (p = 0.032) *Pregnancies:* 9 pregnancies in 7 women (7%) goserelin + chemotherapy 6 pregnancies in 5 women (4%) chemotherapy	*E_2 levels (2-y):* ~500 pmol/L goserelin + chemotherapy ~400 pmol/L chemotherapy *FSH levels (2-y):* ~15 IU/L goserelin + chemotherapy ~23 IU/L chemotherapy (p = 0.001) *LH levels (2-y):* ~18 IU/L goserelin + chemotherapy ~23 IU/L chemotherapy *AMH levels (2-y):* ~0.4 ng/mL goserelin + chemotherapy ~0.2 ng/mL chemotherapy	*2-y OS:* 92% goserelin + chemotherapy 88% chemotherapy
Wang 2021[40]	Prospective study Goserelin 3.6 mg Q4W + neoadjuvant chemotherapy × 4–8 cycles → tamoxifen 20 mg QD × 5 y if HR+ (n = 73) Neoadjuvant or adjuvant chemotherapy × 4–8 cycles (n = 76)	Premenopausal patients ⩽45 y with stage 1–3 breast cancer *ER+:* 67% *PR+:* 62% *HER2+:* 31% (trastuzumab treatment permitted) *Stage 1 or 2:* 87% *Age*, mean (range): 38 y (26–45); *Age <40 y*: 68%	*1-y Recovery:* 70% goserelin + chemotherapy 66% chemotherapy; p = 0.739 *Pregnancies* (goserelin + chemotherapy): 35 desire pregnancy 15 attempted pregnancy 4 pregnancies 1 birth 2 voluntary abortions	*FSH recovery:* 84% goserelin + chemotherapy 66% chemotherapy; p = 0.017 *E_2 recovery:* 69% goserelin + chemotherapy 59% chemotherapy; p = 0.265 *AMH recovery:* 47% goserelin + chemotherapy 22% chemotherapy; OR (95% CI): 3.08 (1.52–6.25); p = 0.002	
Kim 2023[41]	Prospective study Goserelin 3.6 mg Q4W + chemotherapy × 8 cycles (n = 107) Leuprorelin 3.75 mg Q4W + chemotherapy × 8 cycles (n = 86)	Premenopausal women ⩽40 y with stage 1–3 breast cancer *ER+:* 64% *Stage 1 or 2:* 83% *Age*, mean: 34 y	*1-y recovery:* 94% goserelin + chemotherapy 95.3% leuprorelin + chemotherapy	*1-y AMH levels ⩾1 ng/mL:* 50% goserelin + chemotherapy 44% leuprorelin +	

[a]Self-reporting questionnaires to patients recruited from the Stockholm Breast Cancer Study Group.
[b]Administered during chemotherapy, and continued for up to 2 y or until attempting pregnancy for patients with recovery of menstruation.
[c]Defined as FSH in postmenopausal range + amenorrhea × 6 months.
[d]Defined as E_2, FSH, or inhibin B in postmenopausal range + amenorrhea × 3 months.
[e]Started within 1 week of chemotherapy and continued to within 2 weeks of the final chemotherapy.
AMH, anti-Müllerian hormone; CI, confidence interval; DFS, disease-free survival; E_2, estradiol; ER, estrogen receptor; FSH, follicle stimulating hormone; GBG-37 ZORO, German Breast Group ZOladex Rescue of Ovarian function; HR, hazard ratio; LH, luteinizing hormone; mo, months; OR, odds ratio; OS, overall survival; PR, progesterone receptor; Q3–4W, every 3–4 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; QD, once daily; QM, every month; RCT, randomized controlled trial; SD, standard deviation; y, years; ZIPP, Zoladex In Premenopausal Patients.

Table 3. Other adjuvant studies with goserelin in women with early-stage breast cancer.

Author, year	Study design; treatment arms	Patient population	Disease-free survival	OS
Gnant 2009[43] Gnant 2011[44] Gnant 2015[45] ABCSG Trial 12	Randomized, open-label, phase III, multicenter study Adjuvant goserelin 3.6 mg Q4W + zoledronic acid Q4W arm (n = 900) Adjuvant goserelin 3.6 mg Q4W (n = 903) All patients also received either tamoxifen 20 mg QD or anastrozole 1 mg QD	Premenopausal women with stage 1–2, HR+ breast cancer *ER+:* 94% *PR+:* 90% *Stage 1:* 76% *Age ⩽40 y:* 23%	*Median 47.8 mo (4 y):* 94% goserelin + zoledronic acid 91% goserelin; HR (95% CI): 0.64 (0.46–0.91); p = 0.01 *Median 62 mo (5 y):* 92% goserelin + zoledronic acid 88% goserelin; HR (95% CI): 0.68 (0.51–0.91); p = 0.008 *Median 94.4 mo (8 y):* 88% goserelin + zoledronic acid 85% goserelin; HR (95% CI): 0.77 (0.60–0.99); p = 0.04	*Median 47.8 mo (4 y):* 98% goserelin + zoledronic acid 97% goserelin; HR (95% CI): 0.60 (0.32–1.11); p = 0.11 *Median 62 mo (5 y):* 97% goserelin + zoledronic acid 95% goserelin; HR (95% CI): 0.67 (0.41–1.07); p = 0.09 *Median 94.4 mo (8 y):* 97% goserelin + zoledronic acid 95% goserelin; HR (95% CI): 0.66 (0.43–1.02); p = 0.06
Slamon 2024[42] NATALEE	Randomized, open-label, phase III study Ribociclib 400 mg QD + NSAI (letrozole at a dose of 2.5 mg QD or anastrozole 1 mg QD) + goserelin 3.6 mg Q4W in men and premenopausal women (n = 1126) NSAI (letrozole at a dose of 2.5 mg QD or anastrozole 1 mg QD) + goserelin 3.6 mg Q4W in men and premenopausal women (n = 1132)	Pre- or postmenopausal women with stage 2–3, HR+, HER2– early-stage breast cancer N = 5101 *HER2+:* 0% *Age*, median (range): 52 (24–90) *Stage 1–2:* 40% *Neoadjuvant chemotherapy:* 43% *Adjuvant chemotherapy:* 48%	*3-y Invasive:* 90% ribociclib + NSAI + goserelin 87% NSAI + goserelin; HR (95% CI): 0.75 (0.62–0.91; p = 0.003) *3-y Distant:* 91% ribociclib + NSAI + goserelin 89% NSAI + goserelin; HR (95% CI): 0.74 (0.60–0.91)	*30 mo (2.5 y):* 98% ribociclib + NSAI + goserelin 97% NSAI + goserelin; HR (95% CI): 0.76 (0.54–1.07)

ABCSG, Austrian Breast and Colorectal cancer Study Group; CI, confidence interval; ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; mo, months; NSAI, nonsteroidal aromatase inhibitor; PR+, progesterone receptor positive; Q4W, every 4 weeks; QD, once daily; y, years.

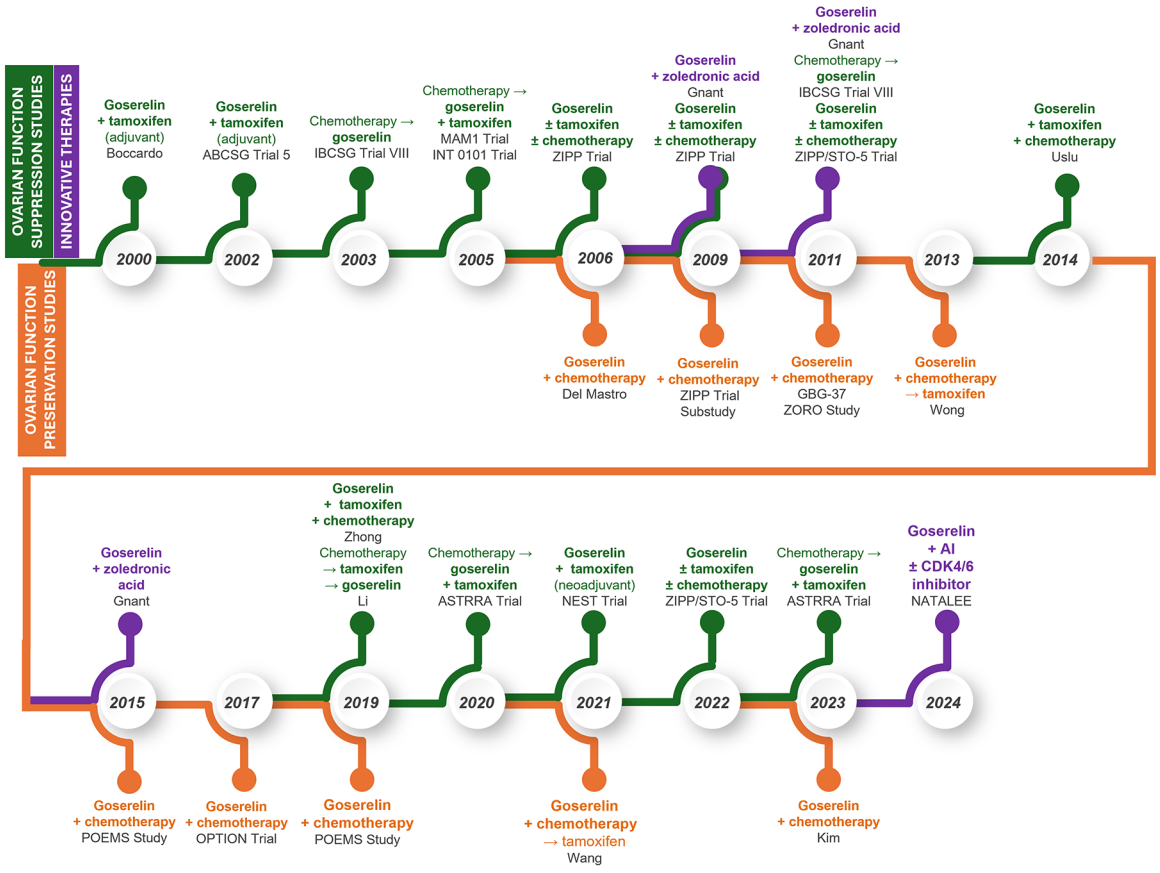

Figure 2. Evolution of goserelin studies.
ABCSG, Austrian Breast and Colorectal cancer Study Group; AI, aromatase inhibitor; ASTRRA, Addition of ovarian Suppression to Tamoxifen in young women with hormone-sensitive breast cancer who Remain premenopausal or Regain vaginal bleeding After chemotherapy; CDK4/6, cyclin-dependent kinase 4 and 6; GBG-37 ZORO, German Breast Group ZOladex Rescue of Ovarian function; IBCSG, International Breast Cancer Study Group; INT, Intergroup; NEST, Neoadjuvant study of chemotherapy versus Endocrine therapy in premenopausal patient with hormone responsive, HER2-negative, lymph node-positive breaST; POEMS, Prevention of Early Menopause; STO-5, Stockholm trial 5; ZIPP, Zoladex In Pre-menopausal Patients.

analysis of the Stockholm cohort demonstrated numerically better 12-year EFS with goserelin (58%) versus tamoxifen (56%) versus goserelin + tamoxifen (53%) versus no endocrine therapy (45%).[22] A similar trend was reported for the 20-year survival analysis based on the distant recurrence-free interval (DFRI) for goserelin versus no endocrine therapy (72% vs 60%; $p = 0.026$).[24]

Out of the four trials evaluating goserelin + tamoxifen following chemotherapy, the Addition of ovarian Suppression to Tamoxifen in young women with hormone-sensitive breast cancer who Remain premenopausal or Regain vaginal bleeding After chemotherapy (ASTRRA) study demonstrated significantly better DFS with goserelin plus tamoxifen versus tamoxifen alone at 5 years (91% vs 88%; $p < 0.033$)[28] and at 8 years (85% vs 80%; $p = 0.003$)[29] (Table 1(d)). OS reached statistical significance at 5 years (99% vs 98%, respectively; $p = 0.029$) but not at 8 years (97% vs 95%, respectively; $p = 0.305$) in the ASTRRA trial, which enrolled 1,282 premenopausal women ⩽45 years of age (Table 1(d)).[28,29] Although statistical significance was not reached for DFS or OS in the Uslu et al study, both were numerically improved for patients receiving goserelin plus tamoxifen compared with tamoxifen alone (Table 1(d)).[27]

A study by Li et al. reported data for switching to 2–3 years of goserelin and anastrazole after chemotherapy and 2–3 years of tamoxifen versus chemotherapy and continuing on tamoxifen for a total of 5 years. This study failed to show the difference

in 2-year DFS and OS in patients who switched to goserelin and anastrazole versus continuing on tamoxifen.[32]

OFP during chemotherapy. Overall, nine publications reported OFP data from eight studies for goserelin in combination with chemotherapy (Table 2).[33–41] The first study was published in 2006 with subsequent studies published over the next two decades (Figure 2).[33–41]

Recovery of menses. Seven studies evaluating chemotherapy plus goserelin for OFP reported recovery rates of menses (Table 2).[33–36,39–41] Menstrual recovery rates increased over time, with 3-month rates at 21%, 6-month rates 33% to 70%, 1-year rates ranging from 36% to 94%, and 2–3-year rates ranging from 93% to 99% (Table 2). The 6-month recovery rate of menses was higher among patients who received goserelin with chemotherapy (33%–70%) rather than chemotherapy alone (6%–57%); the same trend was observed with 1-year recovery rate (36%–83% vs 10%–80%) (Table 2).[34,35,39] Overall menstrual recovery rates were higher (range 89%–94%) among patients ⩽40 years of age than those >40 years old (42%–56%; Table 2).[33,36,39] Younger women also tended to have shorter time (⩽6.1 months) to full recovery of menstruation than older patients (7.9 months; Table 2).[33]

In the Prevention of Early Menopause (POEMS) study, 2-year ovarian failure (8% vs 22%; $p = 0.02$) and 2-year ovarian dysfunction (14% vs 33%; $p = 0.03$) rates were significantly lower with the addition of goserelin to chemotherapy regimen versus chemotherapy alone, respectively (Table 2).[37,38]

Pregnancy outcomes. Successful pregnancies were reported in 5 studies with goserelin in combination with chemotherapy (Table 2).[35–40] Significantly higher 2-year (21% vs 11%; $p = 0.03$) and 5-year (23% vs 12%; $p = 0.03$) pregnancy rates were reported in POEMS for patients receiving goserelin plus chemotherapy versus chemotherapy alone (Table 2).[37,38]

Recovery of hormone levels. Effects on the recovery of hormone levels were reported in 5 studies evaluating patients receiving goserelin plus chemotherapy (Table 2).[33,35,39–41] AMH levels recovered in a higher percentage of patients receiving goserelin than in those without goserelin (47%–50% vs 22%–33%, respectively).[35,40] No significant difference in AMH levels was observed between patients receiving goserelin plus chemotherapy versus leuprolide plus chemotherapy (50% vs 44%, respectively).[41] In general, higher E_2, and lower FSH and LH recovery levels at follow-up were observed in women who had goserelin added to their chemotherapy regimen versus chemotherapy alone (Table 2).[35,39]

Other adjuvant studies with goserelin. With the introduction of bone-modifying agents and CDK4/6 inhibitors, data on the use of goserelin in combination with novel agents in early-stage breast cancer became available in 2009–2015 and 2024, respectively (Table 3 and Figure 2).[42–45] Although these studies were not designed to specifically evaluate the efficacy of goserelin, they illustrate that goserelin has become part of the standard treatment for OFS and has been safely incorporated into modern treatment regimens for early-stage ER+ breast cancer.[42–45]

Goserelin plus bone-modifying agents. The prospective, open-label, phase III randomized controlled ABCSG Trial 12 investigated the efficacy of adding bone-modifying agents to goserelin + an AI or tamoxifen therapy in early-stage breast cancer (Table 3).[43–45] The trial enrolled 1,803 premenopausal women who had undergone primary surgery but no adjuvant chemotherapy.[43,44] All patients received goserelin 3.6 mg Q4W, and either tamoxifen 20 mg once-daily (QD) or anastrozole 1 mg QD, with or without zoledronic acid for 3 years.[43,44] No new safety issues were identified with the use of goserelin with or without zoledronic acid, suggesting that these agents can be used together.

Goserelin with CDK4/6 inhibitors. The prospective, phase III randomized controlled trial NATALEE evaluated the efficacy of adding a CDK4/6 inhibitor to goserelin plus an AI therapy in early-stage breast cancer (Table 3).[42] The trial enrolled 5101 patients and all premenopausal women and men received either letrozole 2.5 mg daily or anastrozole 1 mg daily for 5 years as their AI therapy, along with goserelin 3.6 mg Q4W.[42] Patients allocated to receive CDK4/6 inhibitor were given ribociclib 400 mg QD for 3 years.[42] In an interim analysis with a median follow-up duration of 30 months, the OS was 98% in the CDK4/6 inhibitor plus goserelin + AI group versus 97% in the goserelin + AI alone (HR 0.76 (95% CI: 0.54–1.07)).[42] The 3-year invasive DFS was 90% in the CDK4/6 inhibitor plus goserelin + AI

group versus 87% in the goserelin+AI alone (HR 0.75 (95% CI: 0.62–0.91); $p=0.003$).[42] The 3-year distant DFS was 91% in the CDK4/6 inhibitor plus goserelin+AI group versus 89% in the goserelin+AI alone (HR 0.74 (95% CI: 0.60–0.91)).[42]

Discussion

This large, comprehensive systematic literature review investigated the use of goserelin in combination with endocrine therapy for OFS and with chemotherapy for OFP in pre- and perimenopausal women diagnosed with early-stage breast cancer. Among the studies evaluating OFS, the addition of goserelin to the treatment regimen generally resulted in significant benefits in DFS,[25,26,28,29,31] OS,[20,21] EFS,[20,21] RFS,[18] and recurrence-free survival.[21,22,24] Greater benefits in DFS and OS were reported among women ⩽40 years of age compared with those >40 years of age when goserelin treatment was included.[26,31]

In most trials, the duration of goserelin therapy was 2 years, with the exception of ABCSG Trial 5 (3 years) and INT 0101 trial (5 years; Table 1). Continuing goserelin therapy beyond 5 years is already of interest among healthcare providers and breast cancer survivors.[46] Furthermore, the effect of ovarian suppression due to chemotherapy is of interest and under evaluation.[47,48] The RxPONDER study enrolled early-stage, HR+, HER2-negative lymph-node positive patients with oncotype recurrence score <25 and randomized them to chemotherapy or endocrine therapy.[47] Interestingly, in premenopausal patients, a benefit was seen with chemotherapy regardless of their oncotype recurrence score.[47] Similarly, in the TAILORx study, endocrine therapy was noninferior to chemo-endocrine therapy in the analysis of DFS disease.[48] However, it remains unclear whether this benefit is truly related to chemotherapy or is an effect of chemotherapy's ability to cause ovarian suppression.[47] The role of goserelin in the treatment of early-stage, estrogen receptor-positive (ER+) breast cancer is being further evaluated in the Ovarian Function Suppression Plus Endocrine Therapy (OFSET) trial.[49] In this ongoing randomized phase III trial, pre- and perimenopausal patients with lymph node positive (LN+) disease and oncotype <25 are being randomized to AI + OFS ± chemotherapy.[49] The objective of the OFSET trial is to demonstrate that these patients would not benefit from chemotherapy and that the benefit previously seen with chemotherapy treatment is likely due to OFS which can be achieved with goserelin and other agents.[49]

Fertility and OFP are important aspects of care for many premenopausal women with breast cancer and should be individualized based on various factors including the patient's age and desire for future pregnancy.[50] Younger women may be concerned about breast cancer treatment delays at the time of diagnosis due to efforts to preserve fertility.[50] The combination of goserelin during chemotherapy is a standard strategy for OFP, which has achieved birth rates as high as 24%—a relevant outcome for many women who are interested in avoiding the short- and long-term effects of early menopause.[50] This is also relevant regardless of future pregnancy plans, as patients may realize their desire for pregnancy after completion of chemotherapy treatment.[51] The results of this review showed that OFP with goserelin during chemotherapy resulted in a higher recovery rate of menses within 6–24 months compared with no goserelin treatment.[17,34,35,37–40] More substantial benefits were observed among women ⩽40 years old versus >40 years old.[33,36,39] The addition of goserelin to the treatment regimen also resulted in significantly higher pregnancy rates compared with no goserelin.[37,38] However, despite promising results on pregnancy outcomes, OFP during chemotherapy is not an alternative meant to replace cryopreservation procedures for fertility preservation to increase the chances for future pregnancy, but rather OFP can be pursued in addition to cryopreservation.[50,52]

Goserelin has also been investigated in combination with other agents, including bone-modifying agents and CDK4/6 inhibitors. The ABCSG Trial 12 demonstrated significantly better DFS when the bone-modifying agent zoledronic acid was added to the goserelin + AI/tamoxifen regimen.[43–45] There was a trend toward better outcomes with goserelin plus tamoxifen versus goserelin plus AI, although the study population had a low risk of recurrence.[43–45] Bone health is a critical issue to consider in patients receiving OFS as part of adjuvant endocrine therapy.[52] In the NATALEE trial, the addition of the CDK4/6 inhibitor ribociclib to the goserelin + AI regimen resulted in a significantly higher 3-year DFS compared with no ribociclib in early-stage breast cancer.[42] These trials demonstrated the more modern use of OFS with goserelin as a part of the evolving treatment regimens in early-stage breast cancer.

The adverse events reported in the included studies that were attributable to goserelin were consistent with its known safety profile, with hot flushes, headache, and arthralgia being the most common.[17,18,20,32,33,42,44] Weight gain, thromboembolism, irregular menses, and depression have been reported as Grade 3 or worse among patients receiving goserelin.[30,37] Other adverse events associated with goserelin were generally low grade and not clinically significant, including gastrointestinal (e.g., diarrhea, nausea, stomatitis), neurologic (e.g., mood modification, insomnia) effects, sweating, and vaginal dryness.[26,33] No goserelin treatment-related deaths were reported during follow-up.[17,18,25,26,32,35,42]

The strengths of this systematic review include the rigorous criteria used to evaluate endpoints and the inclusion of only prospective studies. However, there are several limitations to this systematic review. The iterative process in developing the inclusion and exclusion criteria was necessary due to the large number of publications initially identified through the comprehensive literature search. As with many systematic reviews, the collection of articles included represents a variety of study designs, endpoints, and follow-up times between studies. Other limitations include the short follow-up periods of some studies included in the systematic review, particularly in light of the risk of late recurrence among patients with HR+ early-stage breast cancer, the heterogenous distribution of subgroups in some studies, and insufficient adjuvant radiotherapy information. Efforts were made to standardize the representation of deaths reported into OS rates and disease-free events into DFS rates for ease of comparison. Similarly, patient demographics for studies were often reported by the treatment arm, however consolidation of data representing the population of interest (e.g., ER+, stage 1 or 2, age <40 years old) was intentionally done to show the applicability of the data to patients with early-stage breast cancer, as many studies had a mix of early and metastatic disease. While all included studies evaluated only once-a-month goserelin regimen, there are published data on 1- and 3-month formulations.[53–56] There is limited evidence use of goserelin beyond 5 years, and the use of biomarkers as surrogates for efficacy.

Conclusion

This article reports the most up-to-date review of goserelin as OFS as adjuvant endocrine therapy or OFP during chemotherapy in patients with early-stage breast cancer. The findings have shown better outcomes when goserelin was added to both adjuvant endocrine therapy for OFS and chemotherapy for OFP in pre- and perimenopausal breast cancer patients. Overall, this review highlights the substantial benefits of adding goserelin in these settings and its inclusion in more modern treatment regimens with bone-modifying agents or CDK4/6 inhibitors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Competing interests

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Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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