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Investigation of Latest Applications of GnRH Agonists Use in Gynecological Cancers: A Narrative Study

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ABSTRACT

Background & Objective: Gynecological and breast cancers are responsible for a significant proportion of cancer-related mortalities. Recent evidence indicates that 15.25% of the 8.2 million new cancer cases are gynecological malignancies. To enhance patients' prognosis and quality of life, treatment approaches are continuously changing. This study is a narrative review investigating the latest applications of GnRH agonists for treating gynecological malignancies, specifically breast, ovarian, and endometrial cancers.

Materials & Methods: A thorough review of the PubMed, Web of Science, and Google Scholar databases using the keywords 'gonadotropin-releasing hormone agonists', 'GnRH agonists', GnRH analogs', gynecological cancers', 'gynecological malignancies', and 'Breast Cancer' for articles published between 2017 and 2023 was conducted.

Results: Recently, fertility preservation has become a vital concern in modern society. Therefore, GnRH agonists play a key role in protecting the ovarian function of young patients diagnosed with cancer, particularly those with breast or gynecological cancers who are undergoing chemotherapy.

Conclusion: GnRH agonists can play a crucial role in the treatment course of gynecological malignancies, particularly those that are hormone sensitive.

Keywords: GnRH agonist, Gynecologic neoplasm, Breast cancer, Endometrial cancer

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1. Introduction

The second leading cause of death worldwide is cancer, which results in 9.6 million deaths annually (1). Breast cancer is the most prevalent cancer among females around the world, and it is assessed that 75% of them are hormone receptor-positive (HR+) (2). Ovarian carcinoma is the eighth most common malignancy in females worldwide. Ovarian cancer is the second leading cause of cancer-associated death among gynecological malignancies (3). Endometrial cancer (EC) is a common gynecological cancer. It is responsible for >2% of all cancer-related deaths due to cancer (4). The significance of gynecological cancers is not entirely captured in what we have presented, as we have not covered all aspects of these cancers.

Recent evidence indicates that 15.25% of the 8.2 million new cancer cases are gynecological malignancies (1). More than 1.2 million women are diagnosed with cervical, endometrial, and ovarian cancers (5). In Iran, approximately 1659 patients die, and 4060 women are diagnosed with gynecological cancers (GCs) annually, making it an important cause of death as cancer rates increase (5,6). It has been estimated that GCs impose an economic burden of $51 million in Iran (7).

Gonadotropin-Releasing Hormone (GnRH) prompts the pituitary gland to secrete gonadotropins-namely, Luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones play crucial roles in sexual development and reproductive processes (8). GnRH agonists imitate natural hormones, causing an initial increase in gonadotropin secretion. This is then followed by a significant decrease in the production of gonadotropins and sex steroids due to the down regulation of receptors.

The expression of GnRH receptors has been observed in the pathophysiology and therapeutic approaches of diverse gynecological cancers (9). The

presence of GnRH receptors has been observed in the majority of cancers related to the ovaries, endometrium, and breasts **(9)**. According to previous studies, GnRH agonists play a crucial role in the preservation of ovarian function in patients with breast cancer undergoing chemotherapy **(10)**. In addition, GnRH agonists have been employed in the management of hormone-dependent cancers, particularly gynecological malignancies. This is attributed to their capacity to inhibit the secretion of pituitary gonadotropins, which subsequently reduce the production of ovarian estrogen **(11, 12)**.

In this review, we aimed to explore the most recent applications of GnRH agonists in the treatment of gynecological malignancies.

2. Materials and Methods

Given the significant importance and notable prevalence of gynecological cancers, this narrative review aims to investigate the latest advancements in the use of GnRH agonists for treating breast and gynecological malignancies in women. We conducted a thorough review of the PubMed, Web of Science, and Google Scholar databases using the keywords 'gonadotropin-releasing hormone agonists', 'GnRH agonists', 'GnRH analogs', 'gynecological cancers', 'gynecological malignancies', and 'Breast Cancer' for articles published between 2017 and 2023. Articles were initially reviewed by their titles or abstracts, and those deemed unrelated were excluded. Studies that did not focus on gynecological and breast cancers were considered unrelated. Our review included all types of GnRH agonists. The primary cancers under our focus were breast, ovarian, and cervical malignancies. Non-English and non-human studies were excluded. Relevant data from the selected articles, such as the type of GnRH agonist, the type of cancer, and the study's main findings, were extracted for review. The information from these studies was synthesized to provide a comprehensive overview of the latest advancements in the use of GnRH agonists in breast and gynecological malignancies.

3. Results

Multiple studies and clinical trials have evaluated the efficacy of GnRH agonists in oncology. In hormone-dependent cancers, such as breast and endometrial cancers, GnRH agonists have demonstrated significant tumor-suppressive effects. In breast cancer, their combination with tamoxifen or aromatase inhibitors has shown improved disease-free survival, particularly in premenopausal women **(21, 23, 25, 49)**. Similarly, in gynecologic cancers like endometrial and ovarian cancers, GnRH agonists can reduce tumor volume and are useful in fertility-preserving strategies **(31, 35, 48)**.

The primary aim of enhancing women's health during pregnancy and childbirth is to minimize risks and mortality, while preserving future reproductive potential. This involves reducing non-essential cesarean deliveries and safeguarding fertility, particularly in patients receiving treatments such as chemotherapy **(31, 35, 50)**. Several meta-analyses and randomized trials have confirmed that their administration during cytotoxic treatment increases the chances of menstrual recovery and future fertility without compromising survival outcomes **(14-16, 53)**.

4. Discussion

Anti-gonadotoxicity

One of the potential adverse effects of anti-cancer therapies is chemotherapy-induced premature ovarian insufficiency (POI) in women diagnosed with cancer during their reproductive age **(13)**. This complication may cause infertility, menopausal symptoms, and menopausal complications such as osteoporosis, cardiovascular disease, and cognitive disorders **(14)**. Cryopreservation of oocytes or embryos is the standard practice for fertility preservation in patients undergoing anti-cancer therapies during their reproductive age **(15)**.

In recent years, several clinical trials and reviews have been conducted to evaluate the efficiency and safety of GnRH agonists in preserving fertility and gonadal function. Most of these studies suggested that temporary suppression of gonadal activity with GnRH analogs lessens the risk of POI and reduces complications related to POI. Premenopausal patients, especially those with breast cancer, are the best candidates for co-treatment with gonadotropin-releasing hormone agonists and chemotherapy. Clinicians should not rely on GnRH agonist therapy alone to preserve ovarian function. They should utilize this strategy following other standard options such as gamete cryopreservation or in patients who have no access to the fertility unit, refuse, or have a contraindication for surgical techniques. However, data in this setting are conflicting and highly heterogenic **(16-19)**.

Choi et al. **(20)** suggested that transient gonadal suppression via GnRH agonists did not significantly increase menstrual resumption (MR) in malignant ovarian germ cell tumors (MOGCT) after chemotherapy. This may be due to the low rate of POI in MOGCT patients compared to other cancers, such as breast cancer. Some studies have shown that more than 90% of patients with MOGCT obtain MR after anti-cancer treatment, compared to 35% of breast cancer patients after chemotherapy **(20)**.

A retrospective study by Kim et al. **(21)** reported that patients with breast cancer who had ovarian protection by GnRH agonists benefited from ovarian protection compared with those who used chemotherapy alone. They also discovered that GnRH agonist therapy increased disease-free survival and distant metastasis-free survival rates, especially in hormone receptor-positive breast cancers **(21)**.

Zheng et al. concluded that gonadal suppression using GnRH agonists can reduce POI risk but does not affect the therapeutic outcomes of chemotherapy and

post-chemotherapy pregnancy rates **(18)**. Another systematic review by Senra et al. showed that co-treatment with GnRH agonists and chemotherapy reduced post-treatment amenorrhea and POI **(19)**. A clinical trial has shown similar findings **(17)**. According to Senra et al., GnRH agonists may increase spontaneous pregnancy rate after therapy **(19)**.

Female hormones affect HR+ breast cancer cells, causing cancer cell growth. Thus, endocrine therapy can be used for HR+ breast cancer treatment **(22)**.

In some clinical studies, GnRH agonists have been used as adjuvant therapy for HR+, human epidermal growth factor receptor-negative, and lymph node +/- breast cancers instead of chemotherapy, with the same efficacy but lower adverse effects **(23)**.

Most studies were designed to evaluate the anti-gonadotoxic effects of GnRH agonists in patients receiving gonadotoxic agents, such as chemotherapy. For instance, one study suggested that Triptorelin (a GnRH agonist) could be used to prevent or decrease chemotherapy-induced ovarian failure in premenopausal HR + breast cancers **(10)**.

Endocrine treatment is the principal component of endocrine-sensitive early breast cancer in premenopausal patients. Tamoxifen, a selective estrogen receptor modulator (SERM), blocks estrogen receptors. This has dramatically modified the results of adjuvant and metastatic endocrine treatments **(24)**. Some clinical studies showed that GnRH agonists could be effective in endocrine-sensitive or HR+ breast cancer therapy **(23, 25-27).**

Triple-negative breast cancer (TNBC) has the worst clinical presentation among the breast carcinoma subtypes. In recent years, several clinical studies have shown that GnRH agonists are effective in treating TNBC **(28-30)**. Huerta-Reyes et al. concluded that GnRH agonists could reduce breast cancer growth and disease recurrence, especially in patients with TNBC. They also suggested that GnRH analogs could diminish tumor migration **(28)**. Chen et al. found that Leuprolide acetate, which activates GnRH receptors, significantly inhibits the proliferation and metastasis of TNBC. It also increases apoptosis **(30)**. Corona et al. **(29)** reported that GnRH agonists could improve the overall survival of patients with TNBC. These data indicate that GnRH agonists can be targeted in TNBC treatment.

The use of GnRH agonists for fertility preservation has been evaluated in endometrial cancer. The effectiveness of GnRH agonists in preserving fertility post-surgery has been demonstrated in women diagnosed with endometrial intraepithelial neoplasia (EIN) and/or grade 1 endometrial carcinoma **(31)**.

According to the available evidence, GnRH agonists are mainly administered once per month. Thus, a 1-month formulation of GnRH agonists for breast cancer is recommended. **(22, 32)** These injections may cause discomfort for patients and reduce their medication adherence. Two studies evaluated 3-month and 6-month formulations of GnRH agonists. Lee et al. **(23)** investigated 3-month depot GnRH agonists in HR+ breast cancers. They concluded that 3-Month Depot Leuprolide Acetate 11.25 Milligrams and Tamoxifen could suppress ovarian function successfully with no significant adverse effects **(23)**. Wu et al. **(25)** examined the 6-month depot of 22.5-mg leuprolide acetate with a Tamoxifen regimen in HR+ breast cancer patients. During the follow-up periods after ovarian function suppression, none of the individuals menstruated, and all cases had E2 levels < 30pg/ml except in one patient **(25)**.

The European School of Oncology (ESO) and European Society of Medical Oncology (ESMO) guidelines for treating breast cancer in young patients suggest that monthly formulations of GnRH agonists are the preferred option, particularly for women under 35 years of age and those receiving aromatase inhibitors (AI). However, if monthly use is not possible or acceptable to the patient, 3-6 monthly administrations can be considered on a case-by-case basis with close monitoring of ovarian function **(33)**.

Two studies compared the efficacy of bilateral salpingo-oophorectomy (SBO) with GnRH analogs in premenopausal patients with breast cancer. According to a study by Suh et al. **(26)**, patients with HR + breast cancer treated with aromatase inhibitors may benefit from both SBO and GnRH agonists. However, incomplete gonadal function suppression was observed in patients treated with GnRH agonists.

According to the latest ESMO guidelines for metastatic breast cancer, bilateral oophorectomy leads to quicker estrogen suppression than GnRH agonists, which can result in a 2-week tumor flare due to an increase in hormone levels. This may be the preferred option if a rapid response is required **(34)**.

Based on the last ESGO/ESHRE/ESGE Guideline, a combined treatment method that involves first performing a hysteroscopic tumor resection and then administering oral progestins and/or using a levonorgestrel intrauterine device appears to be the most effective fertility-sparing option in patients with endometrial cancer **(35)**. Regarding this guideline, the use of a combined treatment approach that includes hysteroscopic resection followed by either oral or intra-uterine-released progestins or GnRH analogues appears to be a beneficial alternative to traditional fertility-sparing treatments for young women with endometrial endometrioid carcinoma or endometrial hyperplasia. However, GnRH agonists should not be used as first-line therapy **(35)**. Some authors believe that further studies are required to confirm the superiority of SBO over GnRH agonists **(26)**. Another study demonstrated that laparoscopic SBO is more cost-effective than monthly injections of GnRH agonists in hormone-sensitive breast cancer adjuvant therapy **(27)**.

Table 1 represents a summary of studies that have assessed the anti-gonadal toxicity effect of GnRH agonists.

Table 1. **Key studies evaluating GnRH agonists effects for anti-gonadal toxicity**

Study name and year	Study design	Study's objective	Patient characteristics	Treatment arms	GnRH agonist	Results
Lambertini et al.(51) (2019)	Review	Overview of the role of temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients	Premenopausal breast cancer patients who are candidates to undergo chemotherapy	GnRH agonists + Chemotherapy	-	The overall result supports GnRHa protective role in early breast cancers
Abdel-Razeq et al.(52) (2019)	Review	Evaluating the role of temporary ovarian suppression with GnRHa during chemotherapy in early-stage breast cancer patients to preserve ovarian function and fertility	Premenopausal early-stage breast cancer patients who are candidates to undergo chemotherapy	GnRH agonists + Chemotherapy	-	Data on GnRH agonists are conflicting. GnRHa should not be used in place of other proven methods of fertility preservation. GnRHa should be used with other proven methods or when these methods cannot be used.
Lambertini et al. (53) (2018)	Systematic Review and Meta-Analysis	Evaluating the efficacy and the safety of temporary ovarian suppression with GnRHa during chemotherapy in premenopausal patients with early breast cancer	Premenopausal early-stage breast cancer patients who are candidates to undergo chemotherapy	GnRH agonists + Chemotherapy	-	GnRH agonists have a protective role and they can be considered as a strategy to reduce the risk of chemotherapy induced POI in premenopausal early breast cancer patients undergoing (neo-) adjuvant chemotherapy
Kim et al.(54) (2017)	Retrospective study n=101	Evaluating pregnancy rate and menstrual resumption in breast cancer patients receiving GnRHa and chemotherapy	Premenopausal breast cancer patients aged between 20-40 who underwent surgery and adjuvant chemotherapy and	GnRH agonists + Chemotherapy	Leuprorelin 3.75 mg (n=60) and Goserelin 3.6 mg (n=41) SC 2 weeks before chemotherapy and every 28 days until end of chemotherapy s	Fifty percent of patients had successful pregnancy after adjuvant chemotherapy and GnRHa. Further studies are needed.
Leonardo et al.(17) (2017)	prospective, randomized, parallel group study n=202	Evaluating the role of GnRHa for gonadal protection during chemotherapy	Premenopausal early-breast cancer patients undergoing adjuvant or neo-adjuvant chemotherapy	GnRH agonists + Chemotherapy (Cyclophosphamide and/or Anthracycline-containing regimens with or without a Taxane)	3.6mg Goserelin implant or 1-2 weeks before thermotherapy and continuing 3-4 weekly until end of chemotherapy.	GnRHa moderately reduced risk of POI induced by standard adjuvant chemotherapy in early-stage breast cancer patients.
Zheng et al. (18) (2019)	Meta-analysis n=1413	Determining GnRHa efficacy for gonadal protection during chemotherapy and its influence on long term survival rate in patients with cancer	Premenopausal patients with malignancy, SLE, and other diseases receiving chemotherapy	GnRH agonists + chemotherapy		GnRHa reduced risk of chemotherapy induced ovarian dysfunction without manipulating therapeutic outcomes of chemotherapy
Sofiyeva et al.(55) (2019)	Systematic review and Meta-Analysis	Analyzing the anti-gonadotoxicity role of GnRHa in women treated by alkylating agents	Premenopausal individuals undergoing chemotherapy with or without GnRHa co-administration	GnRHa + chemotherapy and Chemotherapy alone		Data suggesting GnRHa administration is an efficient method of decreasing gonadotoxicity of alkylating agents
Meli et al.(56) (2018)	Retrospective observational study n=36	Assessing protective role of Triptorelin against gonadotoxicity effects of chemotherapy	Premenopausal (adolescent) patients receiving chemotherapy for cancer	GnRHa + Chemotherapy	Monthly 3.75 mg Decapeptyl or triple dose of GnRHa (11.25 mg) every three months during chemotherapy	GnRHa co-treatment could prevent POI in patients without HSCT
SENRA et al.(19) (2018)	Systematic review and meta-analysis	Investigating the efficacy of GnRHa co-treatment before and/or during chemotherapy for preserving ovarian function	Premenopausal cancer patients without prior diagnosis of infertility	GnRHa + Chemotherapy or Chemotherapy alone		Evidence supported the use of GnRHa before and/or during chemotherapy to diminish risk of POI. GnRHa also increased spontaneous pregnancy rate in short term
Hickman et al. (57) (2018)	Systematic review and meta-analysis	Evaluating the role of GnRHa for gonadal protection during chemotherapy	Premenopausal cancer patients receiving chemotherapy	GnRHa + Chemotherapy or Chemotherapy alone		GnRHa have a protective role against development of chemotherapy induced ovarian failure
Choi et al. (20) (2020)	Retrospective study n=227	Evaluation of GnRHa role for ovarian function preservation in young patients with malignant ovarian germ cell tumors (MOGCT) during chemotherapy	Premenopausal patients with MOGCT receiving chemotherapy	GnRHa + Chemotherapy or Chemotherapy alone	Leuprolide acetate 3.75 mg, Goserelin acetate 3.75 mg, and Triptorelin acetate 3.75mg SC before chemotherapy and every 4 weeks during chemotherapy	Temporary ovarian function suppression by GnRHa does not increase menstrual resumption MOGCT patients
Kim et al. (21) (2018)	Retrospective study n= 1160	Determining the oncologic effect of a GnRH agonist with chemotherapy for breast cancer patients	Patients aged 20 to 40 years with stage I to III breast cancer who received chemotherapy	GnRHa + Chemotherapy or Chemotherapy alone	Different types of GnRHa SC 1-2 weeks before chemotherapy and every 28 days during chemotherapy	GnRH agonist co-treatment increases disease-free survival and distant metastasis-free survival rate, especially in hormone receptor-positive breast cancers
Suh et al. (26) (2017)	Retrospective study n=66	To compare the efficacy of bilateral salpingo-oophorectomy with GnRHa in HR+ patients treated with AI	Premenopausal patients with Hormone receptor positive HR+, human epidermal growth factor receptor 2- negative HER- , and metastatic breast cancers	bilateral salpingo-oophorectomy versus GnRHa	-	Both strategies were effective inducing gonadal suppression. The clinical outcome was better in BSO. Incomplete gonadal suppression was seen in a subject.
Ferrandina et al. (27) (2017)	Probabilistic decision tree model	To evaluate the cost-effectiveness of GnRHa versus BSO in the adjuvant therapy of breast cancer patients	Patients aged 40-49 years with a history of hormone responsive breast cancers	bilateral salpingo-oophorectomy versus GnRHa	-	BSO was more cost-benefit than GnRHa adjuvant therapy.

GnRHa: Gonadotropin releasing hormone agonist, SC: subcutaneously; HSCT: hematopoietic stem cell transplantation; POI: premature ovarian failure; MOGCT: Malignant ovarian germ cell tumors.

Anti-tumoral Activity of GnRH agonists

Most ovarian cancer tissues show the presence of GnRH receptors, along with receptors for FSH, LH, and estradiol. Binding these ligands to their respective receptors promotes ovarian cell growth **(36-39)**.

GnRH also affects breast cancer, where FSH and LH interact with their receptors in breast cancer cells. This results in alterations to the expression of genes associated with adhesion, movement, and invasion **(40)**. The [D-Lys6]-GnRH analog has been used in some studies because of its resistance to degradation. This analog selectively accumulates in the nuclei of human GnRH receptor-positive cancer cell lines, including breast, ovarian, and endometrial cancer cells **(41, 42)**. Most studies evaluating the antitumor effects of GnRH agonists have been nonhuman and in vivo experiments. Most of these investigations revealed that GnRH agonists could be used as a new and promising therapeutic strategy, especially for breast, ovarian, and prostate cancers, with fewer adverse effects than chemotherapy **(43)**.

A recently conducted retrospective study by Choi et al. presented at the ESMO Congress assessed the oncologic efficacy of GnRH agonists as neoadjuvant therapy for HR+ and HER2-negative breast cancer patients. The study reviewed 431 patients and found that GnRH agonists were more frequently administered to patients under 35 years of age, which was associated with improved Disease-Free Survival (DFS) **(44)**.

Initial studies examining GnRH agonist activity against ovarian tumors have shown moderate efficacy. Later studies showed that high-dose GnRH agonists are more effective against ovarian tumors **(45)**. According to a systematic review by Emons et al. **(45)**, zoptarelin doxorubicin is an efficient and safe cytotoxic compound **(40)**. Phase III trials are needed to discover more about this topic. To date, only two clinical trials have examined the use of GnRH-targeting therapies **(43)**. Further clinical trials are required to confirm this finding.

Prolonged exposure of endometrial cells to exogenous or endogenous estrogen with insufficient progesterone may cause type-1 EC, which accounts for 80% of EC cases **(46)**. Type-1 EC is influenced by hormones and can be cured at an early stage by endocrine therapy without surgery. Beneficial endocrine therapies include estrogen withdrawal and/or large doses of progesterone in patients of reproductive age. Recently, Type 1 EC has been shown to dedifferentiate and does not respond to these treatments sufficiently **(47, 48)**. Type-2 EC does not represent hormone receptors on its surface and are associated with the majority of EC deaths **(47)**.

A systematic review investigated the role of GnRH agonists in the treatment of endometrial cancer **(48)**. EC express GnRH-I receptors on their cell surfaces. Activation of these receptors regulates cell proliferation, cell cycle, and apoptosis. According to preclinical models, GnRH agonists suppress cell proliferation and stimulate apoptosis in human endometrial cancer cell lines **(48)**. Clinical trials have shown that conventional doses of GnRH agonists have marginal efficacy in endometrial cancer, with low toxicity **(48)**. In a study presented at a congress held by ESMO in 2019, it was found that premenopausal women with HR+ metastatic breast cancer who were treated with a combination of Palbociclib, exemestane, and a GnRH agonist had higher Progression-Free Survival (PRS) scores than those who received capecitabine alone. Furthermore, patients reported improved physical functioning with the combined Palbociclib and endocrine therapy **(49)**.

Table 2 provides an overview of recent studies examining the effects of GnRH agonists during the treatment course of gynecological malignancies.

5. Conclusion

Owing to the importance of fertility preservation in society, GnRH agonists can play a promising role in the preservation of ovarian function in patients with cancer undergoing chemotherapy. In addition, it plays a crucial role in the management of gynecological cancers, particularly hormone-dependent cancers.

6. Declarations

Acknowledgments

None.

Ethical Considerations

As this is a narrative review based on previously published studies, no ethical approval or patient consent was required.

Authors' Contributions

M.Y. designed the study, S.M.A. and S. B. and Z. R. and S. H. and A. G. E. collected data. All authors wrote the paper, S. M. A. and M. Y. revised the paper.

Conflict of Interest

All authors declare no conflict of interests.

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Table 2. Key studies evaluating GnRH agonists effects in gynecological cancers

Study name and year	Study design	Study`s objective	Patient characteristics	Treatment arms	GnRH agonist	Results
Venturelli et al. (58) (2018)	Review	To evaluate the role of Triptorelin in early breast cancer treatment	Premenopausal breast cancer patients	GnRHa + (neo)adjuvant therapy	Triptoreline	Various clinical trials approved its effectiveness in the adjuvant treatment of early breast cancer
Wu et al. (25) (2021)	Retrospective study n=228	To evaluate the efficacy of 6-month formulations of LHRHas after surgery	Premenopausal patients with HR+ breast cancer	LHRHa + Tamoxifen + Surgery	6-month formulation of 22.5 mg of leuprolide	The 6-month LHRHa formulation suppressed ovarian function adequately in premenopausal HR+ breast cancer patient
Dellapasqua et al. (59) (2019)	Randomized clinical trial n=51	To compare the effects of neoadjuvant therapy of GnRH agonist versus GnRH antagonist on endocrine responsive breast cancer	Premenopausal women with stage cT2 to 4b, any N, M0; estrogen receptor and progesterone receptor greater than 50%; human epidermal growth factor receptor-2 negative breast cancer	GnRH agonist + Letrozole versus GnRH antagonist (Degarelix) + Letrozole	Triptorelin 3.75 mg IM on day 1 of every cycle plus Letrozole 2.5 mg/day orally	Neoadjuvant therapy of Letrozole with Degarelix achieved OFS more quickly than Triptorelin
Lee et al. (23) (2020)	Retrospective study n=318	To investigate the efficacy of Leuprolide acetate 11.25 mg 3-month depot and Tamoxifen on estradiol levels in breast cancer patients	Premenopausal patients with HR (+) breast cancer	Surgery + Tamoxifen + GnRHa versus Surgery + Tamoxifen	3-month formulation of Leuprolide 11.25mg	3-month formulation of Leuprolide induces gonadal suppression safely and efficiently, while increasing patients' compliance
Chen et al. (30) (2022)	Preclinical study n=224	To evaluate the effects of GnRHa on triple negative breast cancer	Patients with TNBC, HR+/HER2-, and HER2+	GnRH agonist + GnRH antagonist	Cultured cells activated by Leuprolide acetate	GnRH receptor mRNA expression was higher in TNBCs. Higher GnRHa receptor expression is associated with better prognosis. TNBC proliferation and metastasis inhibited by GnRH receptor activation.
Emons et al. (48) (2021)	Systematic review	To investigate the role of GnRHa in endometrial cancer	Patients with endometrial cancer treated with GnRHa	GnRHa	-	GnRHa inhibits proliferation and induces cell apoptosis in the human endometrial cancer line. Clinical trials showed conventional doses of GnRH agonists have marginal efficacy on endometrial cancer with low toxicity.
Gründker et al. (45) (2021)	Systematic review	To investigate the role of GnRHa in ovarian cancer	Patients with ovarian cancer treated with GnRHa	GnRHa	-	Initial studies examining GnRHa activity against ovarian tumors showed moderate efficacy. But, later studies, showed that high-dose GnRH analogs have better efficacies
Tock et al. (31) (2018)	Retrospective study n=18	To examine the efficacy and safety of GnRHa after endometrial resection in patient early-stage EC and/or EIN	Females with grade 1 EC and/or EIN	GnRHa + endometrial resection	3.6 mg Goserelin SC monthly for 3 months or one does of 11.8 mg long acting Goserelin SC	Data supported the efficacy of GnRHas for fertility preservation after surgery in women with endometrial intraepithelial neoplasia (EIN) and/ or grade 1 endometrial carcinoma

GnRHa: Gonadotropin releasing hormone agonist, SC: subcutaneously; HSCT: hematopoietic stem cell transplantation; POI: premature ovarian failure; MOGCT: Malignant ovarian germ cell tumors

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