Odeh *et al. Middle East Fertil Soc J* (2021) 26:42
https://doi.org/10.1186/s43043-021-00088-x

Middle East Fertility Society Journal

REVIEW

Open Access

The use of GnRH analogs in preserving ovarian function during chemotherapy

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Abstract

Background: The literature has always been controversial on the use of gonadotropin-releasing hormone agonists in preserving fertility in women of childbearing age after chemotherapy; thereby, in this article, we will be discussing its use in preserving fertility.

Main body of abstract: When it comes to preserving fertility, it is crucial to consider all available options in this topic due to its very sensitive nature, thereby we have found that while a lot of trials favor the use of gonadotropin-releasing hormone agonists, the lack of proper follow-up and long-term trials renders its use highly debatable, and since the longest follow-up trial showed non-significant results, it also opens the floor for debate on whether this short-term benefit is worth adding another drug to the regimen or not.

Short conclusion: As described in this review, while the use of gonadotropin-releasing hormone agonists is beneficial in a lot of studies, the lack of long-term reports still makes its use debatable, thereby more trials should be done.

Keywords: GnRH agonists, Fertility, Chemotherapy

Background

The management of malignancy in women in their reproductive years may necessitate a surgical, radiological, or a cytotoxic (chemotherapy) approach which exposes the female to dangerous and even toxic doses that will ultimately result in gonadal damage and dysfunction.

Prior to initiating potentially gonadotoxic therapy, physicians should discuss the risk of treatment-induced infertility and possible interventions to preserve fertility [1]. This discussion should occur soon after diagnosis since some interventions to preserve fertility take time and could delay the start of treatment. The ASCO's (*American Society of Clinical Oncology*) *committee* opinion stated in 2006 and reaffirmed in 2013 that as part of education and informed consent before cancer therapy, healthcare providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. The ASCO's committee also stated in 2018 that the guidelines emphasize the use of measures to preserve fertility in young women with cancer, and such measures include assisted reproductive techniques and ovarian protection through the use of GnRH agonists. Although patients may be focused initially on their cancer diagnosis, it is encouraged to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation [2].

This emphasizes the importance of a multidisciplinary approach and collaborative work between oncologists and reproductive medicine specialists in tackling such a crucial and sensitive issue.

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In general, the ovaries of women who receive chemotherapy have a decreased number of primordial follicles which will result even in a greater decrease in the numbers of larger maturing follicles indicating a greater chemotherapeutic effect on follicular development rather than on the oocyte itself. Many young women develop amenorrhea during chemotherapy, and this is what is called chemotherapy-induced amenorrhea which on its own has a significant independent clinical impact (type and dose-dependent) on survival [3]. Reviewing the results of the International Breast Cancer Study Group (IBCSG) Trial VI showed that adjuvant chemotherapy-induced amenorrhea has been shown to be associated with reduced relapses and improved disease-free and overall survival for premenopausal breast cancer patients and is especially significant for node-positive breast cancer [4].

In general, women younger than age 40 years are more likely to retain their menstrual cycles than those older than 40 as they have a larger pool of follicles [5].

Multiple approaches are available for fertility preservation in women undergoing gonadotoxic treatment, these include the following:

1- Cryopreservation of embryos
2- Cryopreservation of mature and immature oocytes
3- Cryopreservation of ovarian tissue
4- Ovarian transposition
5- Gonadal shielding during radiation therapy
6- The use of GnRH analogs in patients with chemotherapy

The efficacy of the use of the GnRH analogs for preserving ovarian function during chemotherapy was always debated in the literature with different findings across multiple randomized controlled trials, with some data regarded as heterogeneous due to the fact that there was no uniform or an absolute definition for premature ovarian failure with many studies referring to amenorrhea as a reflector of ovarian function as well as the scarcity of data on future patient fertility, pregnancy, as well as pregnancy outcomes.

In this review, we will be tackling the issue of the use of the GnRH analogs in preserving ovarian function in patients receiving chemotherapy.

Main text

Biology of GnRH analogs

In 1977, the structure of the GnRH was properly identified by Drs. Guillemin and Schally [6]. A decapeptide (pyro Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) synthesized from a 92-amino acid preprohormone in the preoptic nucleus in the hypothalamus. The portal blood carries the GnRH to the pituitary gland, which contains the gonadotrope cells, where GnRH activates its own receptor, gonadotropin-releasing hormone receptor (GnRHR), to release FSH and LH.

The half-life of GnRH is 2–4 min as it is degraded by peptidase and cleared by glomerular filtration [7], and this was probably the main reason for developing longer-acting agonistic derivatives to increase their duration of action [8]. The GnRH analog causes an initial flare effect that increases gonadotropin levels and causes ovarian stimulation followed by a hypogonadotrophic state within 1–3 weeks of administration [7].

The administration of LHRHa is associated with some adverse effects (e.g., headache, hot flashes, vaginal dryness, sweating, mood changes, insomnia, urogenital symptoms, and thromboembolic events).

Safety concerns regarding its use were raised suggesting a possible increase in the side effects during cytotoxic therapy, a possible detrimental effect of the lack of treatment-induced amenorrhea on prognosis, and a potential negative interaction with chemotherapy.

However, the three available randomized studies [9–11] that investigated the impact of adding concurrent ovarian function suppression to chemotherapy did not demonstrate any difference in patients' prognosis.

Mechanism of action in fertility preservation

In the adult ovary, > 90% of the ovarian reserve is made up of primordial follicles in the resting stage prophase I. Growth initiation of follicles is initially an FSH-independent process and gonadotropin-dependent growth would not occur until later on (antral phase) [12]. Because profound ovarian suppression may take several weeks to achieve, it is unlikely that sufficient lowering of gonadotropins will be achieved within the short time available before the initiation of chemotherapy. Also, if GnRH analogs are given during the follicular phase of the cycle, they may actually cause a flare effect and create the opposite of the desired impact and defeat the purpose of actually suppressing ovarian function during chemotherapy treatment.

This raised many questions regarding how GnRH analogs actually work in fertility preservation.

A proposed intervention in mice showed that gonadotropins enhance caspase-3 and caspase-7 and apoptosis in the theca-interstitial cells of rat preovulatory follicles in culture. The elevations in caspase-3 and caspase-7 activities in theca-interstitial cells were accompanied by an increase in apoptosis [13], since theca-interstitial cells are important for follicle development, this increase in apoptosis might explain the preservation of preovulatory follicles, as this can help them maintain a relatively dormant state. Thus, pituitary desensitization,

induced by GnRH agonist administration, prevents the secretion of growth factors by the FSH-dependent follicles, thus secondarily preserving more primordial follicles in the "dormant" stage and minimizing their unidirectional maturation and ultimate destruction by alkylating agents

Two recent publications found that the proliferation of primordial germ cells is gonadotropin-dependent and is mediated by Akt/phosphatase and tensin homolog deleted on chromosome ten (PTEN) signaling. High concentrations of estrogens stimulate mouse primordial germ cell growth in vitro. Moreover, estrogens stimulate the transcription of the "*Steel*" gene and the production of c-Kit ligand in gonadal somatic cells, and this growth factor is likely to be responsible for the observed stimulation of primordial germ cell growth via an Akt/PTEN pathway [14, 15]. Although the initiation of primordial follicle growth and the early stages of folliculogenesis can occur without gonadotropins, FSH may affect the rate of preantral follicle growth as well; therefore, the assumption that early follicles are gonadotropin independent may need re-evaluation [15–18].

Another proposed modality of action aims to decrease the utero ovarian perfusion created by high estrogen states in the body. High estrogen concentrations significantly increased ovarian perfusion and vessel endothelial area in a rat model of ovarian hyperstimulation, and this effect was significantly and dose-dependently inhibited by administration of a GnRH agonist.

Moreover, it has been shown that human gonads contain independent GnRH receptors. GnRH-I and GnRH-II receptor activation may result in decreased apoptosis. Whether the GnRH agonist effect is direct on the oocyte–cumulus complex or on the granulosa cells themselves, this topic in particular requires further assessment [19].

Another possibility is that GnRH agonists may upregulate an intragonadal antiapoptotic molecule such as sphingosine-1-phosphate (S1P). Tilly et al. [20] have identified several molecules that are required for chemotherapy-induced oocyte apoptosis. While much of their work has relied on mice genes, they have identified a lipid antagonist of the proapoptotic second messenger ceramide, S1P, as a protective molecule [21].

Clinical data

In this review, we will be discussing the use of GnRH analogs in patients with breast cancer and hematological malignancies, since breast cancer is the most common cancer in women, and due to lack of available data, only hematological malignancies were discussed.

Breast cancer

Del Maestro et al. [22] demonstrated that the use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause. The study group looked at the incidence of early menopause in young (aged 18–45) patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy in a randomized controlled trial in 16 sites in Italy where patients were randomized into receiving chemotherapy alone vs chemotherapy and triptorelin administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy. Early menopause was defined as no resumption of menstrual activity and postmenopausal levels of FSH and estradiol 1 year after the last cycle of chemotherapy. The study included hormone receptor-positive as well as hormone receptor-negative breast cancer patients where hormone receptor-positive patients received adjuvant treatment with tamoxifen for up to 5 years. There was no significant difference between the chemotherapy regimens their patients received, either CMF-based (cyclophosphamide, methotrexate, and fluorouracil), anthracycline-based, or anthracycline-taxane-based treatment. With 133 patients randomized to chemotherapy alone and 148 patients randomized to chemotherapy plus triptorelin, the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group ($P = 0.001$) thus an attributable risk reduction of 17% (95% confidence interval, −26% to −7.9%; $P < .001$). In a multivariate analysis, only the treatment with triptorelin was associated with a significant reduction of the risk of developing early menopause with an odds ratio for treatment-related early menopause of 0.28 (95% confidence interval, 0.14 to 0.59; $P < .001$).

Moore et al. [23] demonstrated in a phase 3 trial that ovarian failure rate was significantly less in patients receiving goserelin starting 1 week before the start of the chemotherapy regimen than those in the control group (odds ratio, 0.30; 95% confidence interval [CI], 0.09 to 0.97; $P = 0.04$). Furthermore, after a 5-year follow-up, they also showed that those who received goserelin were more likely to get pregnant than the control group (odds ratio, 2.45; 95% CI, 1.09 to 5.51; $P = 0.03$), without the presence of a difference in pregnancy complications.

In 2012, Munster et al. [24] looked at premenopausal women aged 44 years or younger which were randomly assigned to receive either triptorelin or no triptorelin during neoadjuvant chemotherapy and assessed the preservation of their ovarian function through and after receiving chemotherapy. These patients were stratified by age (< 35, 35 to 39, > 39 years), estrogen receptor status,

and chemotherapy regimen. Premature ovarian failure was defined based on a resumption of menses and serial monitoring of follicle-stimulating hormone (FSH) and inhibin A and B levels. The study targeted 124 patients with a planned 5-year follow-up; however, the trial was stopped for futility after 49 patients were enrolled (median age, 39 years; range, 21 to 43 years); 47 patients were treated according to assigned groups with four cycles of adriamycin plus cyclophosphamide alone or followed by four cycles of paclitaxel or six cycles of fluorouracil, epirubicin, and cyclophosphamide. Menstruation resumed in 19 (90%) of 21 patients in the control group and in 23 (88%) of 26 in the triptorelin group ($P = .36$). Menses returned after a median of 5.8 months (range, 1 to 19 months) after the completion of chemotherapy in the triptorelin vs 5.0 months (range, 0 to 28 months) in the control arm ($P = .58$). Two patients (age 26 and 35 years at random assignment) in the control group had spontaneous pregnancies with term deliveries. FSH and inhibin B levels correlated with menstrual status. The study demonstrated that after patient stratification for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group (10% vs 12% hazard ratio of 0.76 (95% CI, 0.40 to 1.46) indicating no statistically significant advantage of adding triptorelin).

In a randomized, parallel-group study, the Anglo Celtic Group OPTION trial by Leonard et al. [25] which recruited 227 patients, goserelin reduced the prevalence of amenorrhoea between 12 and 24 months to 22% vs 38% in the control group ($P = 0.015$) and the prevalence of POI to 18.5% vs 34.8% in the control group ($P = 0.048$). Follicle-stimulating hormone concentrations were also lower in all women treated with goserelin at both 12 and 24 months ($P = 0.027$, $P = 0.001$, respectively). However, the use in women above the age of 40 proved to be non-significant, further strengthening the evidence supporting the use of GnRHa, but that still does not deny the fact that longer-term outcomes are yet to be studied and that the efficacy in preserving ovarian function is still limited.

A meta-analysis on 14 RCTs [26] showed that the use of GnRHa is favorable as it significantly reduced the risk of POF when given during chemotherapy (OR 0.36, 95% CI 0.23–0.57, $P < 0.001$). Only 5 studies out of the 14 RCTs studied post-chemotherapy pregnancies, which was also deemed significant (OR 1.83, 95% CI 1.02–3.28, $P = 0.041$). This calls for more trials to study the pregnancy rates after chemotherapy, as the current literature does not have much information on this specific variable.

Another meta-analysis done by Lambertini et al. [27] on 5 trials supported the use of GnRHa, but an interesting fact is that they also stated that a younger age (< 40 years) at diagnosis was a significant variable (adjusted OR, 0.35; 95% CI, 0.24–0.52; $P < 0.001$) when it came to the reduction of risk of developing chemotherapy-induced premature ovarian insufficiency (POI), thereby concluding that age is a major variable when it comes to the success of the use of GnRHa in the prevention of chemotherapy-induced POI.

One of the trials supporting the use of triptorelin, the PROMISE trial [28], specifically when it comes to the long term, which is one of the points that makes the use of GnRH agonists debatable, but it is worth mentioning that they also concluded that it does not affect pregnancy rates. The variable found significant was menstrual resumption at 5 years between the GnRHa and control group, 1.28 (95% CI, 0.98–1.68; $P = 0.07$) (Table 1).

Hematological malignancies

Salama et al. [29] in a review addressed preserving fertility in female patients with hematological malignancies, in which they have discussed the use of GnRH agonist along with a lot of other methods. Given that they have stated that the use of GnRH agonists is debatable, it is worth noting that they have stated that it is not suitable for use in prepubertal females due to inactive HPO axis, does not require a delay in cancer treatment, should be carried out before and during chemotherapy, and that it does not protect against the gonadotoxic effects of radiotherapy. However, it was listed as debatable due to contradictory results.

In another retrospective cohort study, triptorelin (Decapeptyl) was administered monthly to 61 women with Hodgkin lymphoma who were under treatment from 1994 to 2006. And out of these 61 women, 50 recovered regular menses, and after the completion of treatment, 13 patients conceived successfully. Falorio et al. [30] concluded that the use of GnRHa may be useful in preventing ovarian damage and infertility in young women receiving polychemotherapy alone or in combination with subdiaphragmatic radiotherapy, but it is not effective in refractory or relapsed patients, since they have found a clear correlation between age at the time of treatment, advanced disease, cumulative therapeutic load, and ovarian failure.

Another study including data from more than 20 years ago was carried out by Driul et al. [31], where they aimed to assess ovarian function in those receiving GnRHa compared to those who did not in a case-control study in survivors of hematological malignancies, where they analyzed 124 patients between 1998 and 2007. The results showed that in those treated with GnRHa, 33% had post-treatment amenorrhea and 6% post-treatment pregnancies, compared to 49% and 4%, respectively, in the control group; however, they have

Table 1 Use of GnRHa in patients with breast cancer

References	Objectives	Chemotherapy regimen	Main findings	Limitations
Del Maestro et al. [22]	Investigating the effect of triptorelin-induced temporary ovarian suppression during chemotherapy on the occurrence of chemotherapy-induced early menopause	100 mg/m^2 of oral cyclophosphamide on days 1–14 or 600 mg/m^2 of intravenous cyclophosphamide on days 1 and 8, 40 mg/m^2 of methotrexate on days 1 and 8, and 600 mg/m^2 of fluorouracil on days 1 and 8 chemotherapy	The rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group ($P = 0.001$) thus an attributable risk reduction of 17% (95% confidence interval, − 26% to − 7.9%; $P < .001$). In a multivariate analysis, only the treatment with triptorelin was associated with a significant reduction of the risk of developing early menopause with an odds ratio for treatment-related early menopause of 0.28 (95% confidence interval, 0.14 to 0.59; $P < .001$).	Lack of follow-up to assess the end points.
Moore et al. [23]	Effect of using Goserelin on the incidence of ovarian failure Outcomes of pregnancy after 5 years	3 to 4 cycles [about 3 months] or 6 to 8 cycles [about 6 months] and anthracycline-based vs nonanthracycline-based	Ovarian failure rate was 8% in the goserelin group and 22% in the chemotherapy-alone group (odds ratio, 0.30; 95% confidence interval [CI], 0.09 to 0.97; $P = 0.04$) Among the 218 patients who could be evaluated, 34 (16%) had at least one pregnancy: 12 of 113 (11%) in the chemotherapy-alone group and 22 of 105 (21%) in the goserelin group (odds ratio, 2.45; 95% CI, 1.09 to 5.51; $P = 0.03$).	The study included only patients with ER-negative disease.
Munster et al. [24]	Effect of triptorelin on the preservation of ovarian function through and after receiving chemotherapy	Four cycles of adriamycin plus cyclophosphamide alone or followed by four cycles of paclitaxel or six cycles of fluorouracil, epirubicin, and cyclophosphamide	Menstruation resumed in 19 (90%) of 21 patients in the control group and in 23 (88%) of 26 in the triptorelin group ($P = .36$). Menses returned after a median of 5.8 months (range, 1 to 19 months) after the completion of chemotherapy in the triptorelin vs 5.0 months (range, 0 to 28 months) in the control arm ($P = .58$). Two patients (age 26 and 35 years at random assignment) in the control group had spontaneous pregnancies with term deliveries. After patient stratification for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group (10% vs 12% hazard ratio of 0.76; 95% CI, 0.40 to 1.46) indicating no statistically significant advantage of adding triptorelin.	Small sample size.

Table 1 (continued)

References	Objectives	Chemotherapy regimen	Main findings	Limitations
Leonard, et al. [25]	Assess amenorrhoea between 12 and 24 months after the use of goserelin	Six to eight cycles of cyclophosphamide and/or anthracycline-containing regimens with or without a taxane	Goserelin reduced the prevalence of amenorrhoea between 12 and 24 months to 22% vs 38% in the control group ($P = 0.015$) and the prevalence of POI to 18.5% vs 34.8% in the control group, respectively ($P = 0.048$). Follicle-stimulating hormone concentrations were also lower in all women treated with goserelin at both 12 and 24 months ($P = 0.027$, $P = 0.001$, respectively). However, the use in women above the age of 40 proved to be non-significant.	Small sample size.
Lambertini et al. [26]	Effect of use of triptorelin on the risk of premature ovarian failure and number of pregnancies after breast cancer treatment	N/A	A significant reduction in the risk of POF (OR 0.36, 95% CI 0.23–0.57, $P < 0.001$) was observed in patients receiving the agonist during chemotherapy, although with significant heterogeneity ($I^2 = 47.1\%$, P (heterogeneity) = 0.026). Of the 359 patients treated with GnRH analog during chemotherapy, 33 (9.2%) became pregnant, compared with 19 (5.5%) among 347 women undergoing chemotherapy alone which was statistically significant (OR 1.83, 95% CI 1.02–3.28, $P = 0.041$) with no heterogeneity.	Different definitions of premature ovarian failure used, few studies including end point data, and data analyzed not from individual patient-level data.
Lambertini et al. [27]	Effect of use of GnRHa on chemotherapy-induced premature ovarian failure	N/A	In the GnRHa group, 51 (14.1%) of 363 patients developed premature ovarian insufficiency (POI), as compared with 111 (30.9%) of 359 in the control group (adjusted OR, 0.38; 95% CI, 0.26–0.57; $P < 0.001$) without any heterogeneity. The multivariate analysis showed that only treatment with GnRHa (adjusted OR, 0.38; 95% CI, 0.26–0.57; $P < 0.001$) and younger age at diagnosis (< 40 years) (adjusted OR, 0.35; 95% CI, 0.24–0.52; $P < 0.001$) were significantly associated with a reduced risk of developing chemotherapy-induced POI.	Individual patient-level data from only five major randomized trials were included.

Table 1 (continued)

References	Objectives	Chemotherapy regimen	Main findings	Limitations
Lambertini et al. [28]	Effect of administration of triptorelin on ovarian function recovery and rate of pregnancy	FE60-75-100C every 21–28 days CMF every 28 days A—>CMF EC—>paclitaxel FE—>paclitaxel EC—>docetaxel	Premenopausal women do actually benefit from the administration of triptorelin along with chemotherapy specifically in terms of higher long-term probability of ovarian function recovery; however, without a statistically significant difference in pregnancy rate, the incidence of menstrual resumption at 5 years was 72.6% (95% CI, 65.7–80.3%) among the 148 patients in the GnRHa group and 64.0% (95% CI, 56.2–72.8%) among the 133 patients in the control group (hazard ratio (HR), 1.28; 95% CI, 0.98–1.68; $P = 0.07$).	Analyses not prespecified in the study protocol, long-term outcome collection was planned at the time of primary end point analysis.

concluded that there was no statistical significance to emphasize on the use of GnRHa and that more evidence should be obtained.

A retrospective cohort study compared 286 patients who received GnRH agonist with chemotherapy and 188 patients who were treated with chemotherapy alone, and in this study, the primary outcome was spontaneous pregnancies. The secondary outcome was cyclic ovarian function (COF) vs premature ovarian failure (POF). These outcomes were assessed 2 years or more after chemotherapy. Blumenfeld et al. [32] concluded that spontaneous conception is significantly achieved in the intervention group ($P = .0004$, OR 3.12, 95% CI 1.7–5.8), and adding to that preservation COF ($P = .0001$), thereby adding to the literature in supporting the use of GnRHa. Furthermore, 123 healthy newborns were born in the intervention group, compared to 40 in the control group.

In a prospective non-randomized case-control study, Blumenfeld et al. [33] elaborated on the effect of co-treatment with GnRHa on ovarian damage and concluded that it may reduce ovarian damage significantly. This study recruited 115 female patients with Hodgkin lymphoma, where 65 patients received a monthly injection of GnRHa throughout and before starting chemotherapy, up to a maximum of 6 months. The results showed that the resumption of regular menses was significantly seen in the intervention group; however, no significance was seen on the preservation of COF, which contradicts previous studies, and these results further emphasize the need for more trials on the use of GnRHa.

Taking it a step further, in a study aiming to compare the rate of POF after stem cell transplantation (SCT) in women receiving GnRHa in conjunction with gonadotoxic chemotherapy, Blumenfeld et al. [34] showed that in 83 patients, 18 out of the 47 patients receiving GnRHa resumed cyclic ovarian function, compared with 4 out of the 36 not receiving GnRHa. There were no significant differences in age, chemotherapy treatment, or diagnoses between the study and control groups. They concluded that GnRHa cotreatment in conjunction with conditioning chemotherapy before SCT may significantly decrease the gonadotoxicity and POF from 82 to 33% in lymphoma but not in leukemia patients.

On the other hand, Demeestere et al. [35] showed that even though on the short term, the ovarian function might be better in a group receiving GnRHa when compared to a control group (3.14 ± 0.80 ng/mL at inclusion vs 1.26 ± 0.3 ng/mL after 2 to 4 years, $P = .039$); this significance was no longer seen when it came to a long-term follow-up (1.58 ± 0.38 ng/mL, $P = .520$). In their study, they signified the fact that more trials should be done to assess the long-term effects of the use of GnRHa in preserving fertility, and this calls for the discussion of whether this short-term improvement is worth the addition of GnRHa or not (Table 2).

Conclusions

As described in this RCT review, the issue of GnRH analogs is still highly debatable in the literature with conflicting evidence and heterogeneous data.

The reason behind the heterogeneity of data may arise from the lack of a consistent uniform definition of premature ovarian failure following chemotherapy, with a clear focus on the resumption of menses as a primary indicator of resumed ovarian function. Focus on pregnancy outcomes as well as survival rates were never the primary outcomes in any of the studies which looked at the role of the use of GnRH analogs in ovarian function preservation. In the above most recent meta-analysis [24], there was an inclusion of RCTs with small patient populations that may not reflect back properly on the general population and may not be strong enough to influence any change in recent guidelines and consensus about using GnRH analogs in young patients receiving chemotherapy.

The administration of GnRH analogs in patients receiving chemotherapy offers a more accessible option for patients and can be used in conjunction with traditional fertility preservation techniques; it also offers feasibility in regard to cost, timing issues, and the need for a partner.

The American Society of Clinical Oncology Clinical Practice Guidelines (2013) regard sperm and embryo cryopreservation as well as oocyte cryopreservation as standard practice with other fertility preservation methods, including the use of GnRH analogs, considered investigational and should be performed by providers with the necessary expertise. Yet, in 2015, the St. Gallen International Expert Consensus panel and the National Comprehensive Cancer Network (NCCN) guidelines have been updated to acknowledge the role of luteinizing hormone-releasing hormone agonists (LHRHa) in preventing chemotherapy-induced POF of hormone receptor-negative breast cancer.

Moreover, in hormone receptor-positive breast cancer patients, the issue of the concurrent use of endocrine therapy, namely tamoxifen along with chemotherapy has demonstrated to be of inferiority in regard to disease-free survival when compared to a sequential administration [30] due to potential antagonism between tamoxifen and the cytotoxic agent. Yet, recently reported excellent survival results with triptorelin administered concurrently with chemotherapy in the Tamoxifen and Exemestane Trial [36] suggests that the use of GnRH agonist may also have a role in improving survival. This overall reflects a hesitant opinion to recommend this technique.

Table 2 Use of GnRH agonists in patients with hematological malignancies

References	Objectives	Main findings	Limitations
Salama et al. [29]	Preserving fertility in female patients with hematological malignancies	Given that they have stated that the use of GnRH agonists is debatable, it is worth noting that they have stated that it is not suitable for use in prepubertal females due to inactive HPO axis, does not require a delay in cancer treatment, should be carried out before and during chemotherapy, and that it does not protect against the gonadotoxic effects of radiotherapy.	Systematic review not focusing on the use of GnRH agonists alone
Falorio et al. [30]	Effect of use of GnRH agonists in patients with hematological malignancies on preserving fertility	Out of 61 women, 50 recovered regular menses, and after the completion of treatment, 13 patients conceived successfully.	Small sample size
Driul et al. [31]	Assessment of ovarian function in those taking GnRH agonists against those who do not	The results showed that in those treated with GnRHa, 33% had post-treatment amenorrhea and 6% post-treatment pregnancies, compared to 49% and 4%, respectively, in the control group; however, they have concluded that there was no statistical significance to emphasize on the use of GnRHa and that more evidence should be obtained.	Not done in a recent date
Blumenfeld et al. [32]	Effect of GnRH agonists on spontaneous pregnancies and ovarian function	87% (127 of 146) of the patients in the GnRHa group retained COF and 13% (19 of 146) suffered POF, whereas in the control group, 49% (35 of 71) experienced COF and 51% (36 of 71) suffered POF ($P = .0001$). The odds ratio (OR) for preserving COF was 6.87 for the patients who received GnRHa (95% confidence interval [CI] 3.4–13.4). Overall, 60% (112 of 188) of the survivors conceived: 69.3% (84 of 122) of the patients in the GnRHa group compared with 42.4% (28 of 66) in the control group ($P = .006$). In the GnRHa group, 123 healthy newborns were delivered, vs 40 in the controls. Spontaneous pregnancies occurred in 65.6% (80 of 122) of the survivors in the GnRHa group vs 37.9% (25 of 66) in the control group ($P = .0004$, OR 3.12, 95% CI 1.7–5.8).	Retrospective nature
Blumenfeld et al. [33]	Effect of cotreatment with GnRHa on ovarian damage	The results showed that in the GnRHa/chemotherapy group, 63 out of 65 patients resumed ovulation and regular menses (96.9 %), compared with 63% of the 46 control subjects. Twenty of the 22 patients in the BEACOPP/escalated BEACOPP/GnRHa cotreatment resumed cyclic ovarian function vs 9 of the 14 in the chemotherapy-only group. All 17 MOPP/ABV/GnRHa-cotreated patients resumed COF vs 11 of the 22 in the chemotherapy-only group. Eventually, they concluded that there was no significant effect of the GnRHa cotreatment regarding COF in the ABVD group	Non-Randomized trial
Blumenfeld et al. [34]	Assessment of the rate of POF after stem cell transplantation in women receiving GnRHa in conjunction with gonadotoxic chemotherapy	In 83 patients, 18 out of the 47 patients receiving GnRHa resumed cyclic ovarian function, compared with 4 out of the 36 not receiving GnRHa.	Small sample size
Demeestere et al. [35]	Effect of GnRH agonist administration and ovarian function preservation	37 patients who had AMH levels available at least once during the follow-up period, the mean AMH values decreased significantly after treatment (3.14 ± 0.80 ng/mL at inclusion vs 1.26 ± 0.3 ng/mL after 2 to 4 years, $P = .039$) and remained at a similar level after 5 to 7 years (1.58 ± 0.38 ng/mL, $P = .520$). A higher rate of low AMH (AMH < 0.5 ng/mL) was observed in both groups after 2 to 4 years of follow-up.	Small sample size

Abbreviations
GnRHa: Gonadotropin-releasing hormone agonist/analog; COF: Cycling ovarian function; POF: Premature ovarian failure; LHRHa: Luteinizing hormone-releasing hormone analog; POI: Premature ovarian Insufficiency.

Acknowledgements
Not applicable.

Authors' contributions
S.G, the corresponding author, ensured that the entire group is fully aware of the best practices in the discipline of publication and the full author list and order. O.O finalized the manuscript; in addition to that, all authors have read and approved the final manuscript, contributed substantially in the drafting and revision of the review. Furthermore, all authors have agreed to be personally accountable for the author's own contributions and that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Received: 18 June 2021 Accepted: 20 October 2021
Published online: 01 November 2021

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