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Conservative management of reproductive cancers. Ovarian protection during treatment



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A B S T R A C T

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Globally, breast cancer is the most common female reproductive cancer. Although alkylating chemotherapy is not part of initial curative-intent treatment in women with other reproductive cancers, it is often used to treat women with curable breast cancer. Chemotherapy-associated ovarian failure (COF) is a potential consequence of this treatment and can cause infertility and increase the risk of cognitive impairment, cardiovascular disease and fractures from reduced bone mineral density.

Although cryopreservation of embryos and oocytes is often effective for fertility preservation, this does not prevent COF and its associated complications. Randomised trials, predominantly of women undergoing alkylating chemotherapy for breast cancer, have shown evidence for the efficacy of gonadotropin-releasing hormone agonists (GnRHa) in reducing the risk of COF. Concurrent GnRHa use should be considered for all premenopausal women planned to commence alkylating chemotherapy for curable cancer, regardless of their childbearing status, to further improve survivorship for women diagnosed with cancer.

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Introduction

Female reproductive cancers include cancers of the breast, ovary, cervix and endometrium, as well as uncommon cancers such as vulvar, vaginal, fallopian tube cancers and choriocarcinomas [1]. Breast cancer is the most common female reproductive cancer, with 266,120 estimated new cases diagnosed in the United States in 2018 [2,3]. Approximately 30% of these new cases will be diagnosed in premenopausal women [3]. Furthermore, an additional 30,000 premenopausal women will be diagnosed with a reproductive cancer other than breast cancer in 2018 [4–6]. As survival rates for reproductive cancers improve [3–6] survivorship considerations are increasingly important in these young women.

Multimodal therapy, including surgery, radiation and cytotoxic chemotherapy, is often used in the curative-intent treatment for female reproductive cancers. One major potential long-term adverse effect of this therapy is premature ovarian failure (POF). In studies of early-stage cervical and ovarian cancers, fertility-sparing surgery has been shown to preserve fertility without comprising long term cancer outcomes [7–16] and this surgery is currently recommended in the 2018 American Society of Clinical Oncology (ASCO) guidelines [17].

Alkylating chemotherapy such as cyclophosphamide is commonly used to treat potentially curable breast cancer. In other reproductive cancers, initial curative intent systemic therapy often includes either platinum-based or taxane-based chemotherapy, or a combination of both. Alkylating chemotherapy is associated with chemotherapy-associated ovarian failure (COF), and the risk of COF is increased with higher cumulative dose of the alkylating agent and with increasing age [18]. Less is known about the effect of non-alkylating chemotherapy on ovarian function. Platinum-based chemotherapy such as cisplatin has been shown to impair steroidogenesis and promote apoptosis in human granulosa-luteal cells (GLC) incubated with varying concentrations of cisplatin for 48 hours [19]. DNA damage was also observed in the ovaries of rats exposed to intraperitoneal carboplatin [20], and intraperitoneal carboplatin has been shown to deplete approximately 50% of primordial follicles in mice [21]. There is limited information regarding the rate of COF due to platinum-based chemotherapy in humans; however, small studies suggest that it affects ovarian function [22].

COF can significantly impact the health and well-being of women with cancer. Infertility is a recognised consequence of ovarian failure. Ovarian failure is also associated with an increased risk of fracture (because of reduction in bone mineral density [BMD]), cardiovascular disease, cognitive dysfunction, sexual dysfunction and decreased quality of life [23–25]. Prevention of COF is therefore very important to improve the survivorship experience for young women, regardless of their childbearing plans.

Current measures to preserve fertility include oocyte and embryo cryopreservation and ovarian tissue cryopreservation. However, these methods do not preserve gonadal function and thus do not reduce the long-term sequelae of premature menopause other than infertility. Studies, predominantly in patients with breast cancer, have shown that concurrent administration of gonadotropin-releasing hormone agonists (GnRHa) substantially reduces the risk of COF. Because of this, the use of GnRHa in this setting is recommended in the European St Gallen and U.S. National Comprehensive Cancer Network guidelines for premenopausal women with breast cancer [26,27].

This chapter summarises the evidence for ovarian protection during alkylating chemotherapy treatment, addressing both fertility preservation as well as ovarian function preservation.

Chemotherapy-associated ovarian failure

In the human ovary, a fixed number of primordial follicles are present at birth [28]. During a woman's reproductive life, these follicles mature through ovulatory cycles and decline in number, until menopause [28].

Alkylating agents, such as cyclophosphamide, cause DNA breaks and, eventually, the apoptosis of the cancer cell [29]. In the premenopausal ovary, alkylating agents are thought to cause death of mature ovarian follicles through a similar mechanism [29]. Death of mature follicles results in a reduction in oestrogen levels. Through a negative feedback mechanism, this prompts an increase in follicle-stimulating hormone (FSH) secretion and subsequent accelerated activation of primordial ovarian follicles [29]. These primordial follicles mature and subsequently undergo apoptosis when

exposed to alkylating agents [29]. This cycle can result in burnout of both mature and primordial ovarian follicles, and thus ovarian failure [29].

Unlike spontaneous menopause, ovarian function can resume in some women after chemotherapy even following a prolonged period of amenorrhoea and elevated gonadotropin levels [30]. Therefore, defining COF in this population is difficult, and the terms and definitions used to describe COF vary in the literature. Definitions and study endpoints generally include either amenorrhoea or FSH levels in the postmenopausal range, or a combination of both amenorrhoea and elevated FSH. Recently, there has been interest in serum levels of anti-Mullerian hormone (AMH) as a measure of ovarian reserve. Although AMH is not directly produced by primordial follicles, its levels appear to correlate with the number of primordial follicles and hence ovarian reserve [31]. AMH has not been widely used in the randomised controlled trials addressing the prevention of COF, and thus, its interpretation is limited in this setting. The terminology used in the relevant trials included treatment-related early menopause, premature ovarian insufficiency (POI) and POF. For consistency, the term COF is used throughout this review.

COF can cause symptoms related to oestrogen deficiency such as hot flushes, night sweats and vaginal dryness [25,32]. Depressive symptoms, fatigue, weight gain and significant decreases in BMD have also been reported in breast cancer patients with COF [24,25,32,33]. In non-cancer patients, ovarian failure before the age of 40 years, from both surgical and non-surgical causes, is associated with worse cognitive function in later life [34]. An American cohort study observed that women who underwent prophylactic bilateral oophorectomy before the age of 50 years were at a higher risk of mortality than age-matched women who had not undergone oophorectomy (hazard ratio [HR] 1.67, 95% confidence interval [CI]: 1.16–2.40, $p = 0.006$) [23]. These women were also at a higher risk of multi-morbidity including hyperlipidaemia, cardiovascular disease, depression, osteoporosis, arthritis and chronic obstructive pulmonary disease [23]. Therefore, prevention of COF is important to avoid these long-term health outcomes.

Fertility preservation

The American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) recognise embryo and oocyte cryopreservation as the main fertility preservation methods in premenopausal, post-pubertal women undergoing chemotherapy [17,35]. Embryo cryopreservation requires a male partner or use of donor sperm, whereas oocyte cryopreservation does not [36]. Vitrification of embryos or oocytes has shown higher cryo-survival rates than slow freezing, and thus, it is the current standard of care [37]. However, the process of controlled ovarian stimulation, ovum pickup and vitrification requires time, and chemotherapy often needs to be delayed by at least 10 to 12 days [38].

In pre-pubertal women, and in patients who cannot delay chemotherapy, ovarian tissue cryopreservation can be used [36,39]. Ovarian tissue is collected surgically by laparoscopy and cryopreserved by slow freezing [36,39]. This tissue is later thawed and the woman undergoes either in vitro fertilisation and embryo transfer, or ovarian tissue reimplantation by orthotopic transplantation [36,39]. This method remains experimental with only 130 live births reported at the end of June 2017 [36]. This method also carries a risk of reimplanting malignant cells along with the graft tissue [40]. Therefore, ovarian tissue cryopreservation is not currently considered as standard practice for fertility preservation.

Although cryopreservation methods are often effective for fertility conservation, they do not protect ovarian function. Women may ultimately prefer a natural conception only achievable if COF is avoided. Prevention of COF may also reduce the long-term health sequelae of ovarian failure, an aim that cannot be achieved by cryopreservation alone. Therefore, fertility preservation methods and prevention of COF should occur concurrently, rather than exclusively.

Preventing chemotherapy-associated ovarian failure

GnRHa used concurrently with alkylating chemotherapy have been shown to be effective in the prevention of COF in premenopausal women with breast cancer [41–44]. There are no randomised controlled trials investigating the use of GnRHa in the setting of platinum-based or taxane-based

chemotherapy. Furthermore, evidence for GnRHa use in reproductive cancers other than breast cancer is limited.

Gonadotropin-releasing hormone (GnRH), secreted in a pulsatile manner into the hypothalamo-hypophyseal circulation, regulates the release of luteinising hormone (LH) and FSH from the anterior pituitary, which promotes ovarian follicle development and ovulation [45]. Sustained exposure to GnRHa initially causes transient stimulation of LH and FSH release [46]. This is then followed by FSH and LH suppression due to desensitisation of GnRH-mediated secretion, thereby producing reversible biochemical castration [46].

The exact mechanism by which GnRHa protect ovarian function is not fully understood. The major proposed mechanism is the interruption of accelerated recruitment and apoptosis of follicles by reducing FSH secretion, but a number of alternative mechanisms have also been hypothesised [47]. In female Rhesus macaques, GnRHa have been shown to reduce the daily rate of follicular decline and the total number of follicles lost during chemotherapy [48]. In humans, most data for GnRHa use concurrently with alkylating agents for the prevention of ovarian failure are from women with breast cancer and lymphoma [41–43,49,50,51].

Pregnancy was a secondary endpoint in several of these studies. Pregnancy rates in the trials overall were low as would be expected for women with a diagnosis of cancer, and intention to have further offspring was not a criterion for trial participation. Many of these women likely did not intend pregnancy, either because of concerns about their cancer prognosis, ongoing cancer treatment that contraindicated pregnancy or simply because they had completed childbearing before their cancer diagnosis.

The efficacy of GnRH antagonists in the prevention of COF has been less well investigated. Unlike GnRHa, where there is an initial surge in FSH and LH one week after first administration, GnRH antagonists result in immediate suppression of gonadotropins. This may be advantageous when chemotherapy is required urgently. The combination of GnRHa and GnRH antagonist has been shown to provide suppression of gonadotropin secretion within 96 hours in treated patients [52,53], allowing the commencement of chemotherapy without delay. However, one major disadvantage of GnRH antagonists is the frequency of administration, with cetorelix administered daily and degarelix administered monthly by subcutaneous injection.

A number of studies in cyclophosphamide-treated rats have investigated the efficacy of GnRH antagonists in preventing COF [54–57]. The definition of COF varied between studies. Common endpoints included live birth rate and number of primordial ovarian follicles. The most recent study by Knudston and colleagues in 2017 investigated the effect of GnRH antagonist in combination with GnRHa on the live birth rate of cyclophosphamide-treated rats compared to GnRHa alone or placebo [54]. This study demonstrated that rats exposed to cyclophosphamide without GnRHa or GnRH antagonist had a lower live birth rate [54]. Rats who received a GnRHa or a GnRHa in combination with a GnRH antagonist had a live birth rate similar to that of rats that did not receive cyclophosphamide [54]. Another study with rats treated with cisplatin investigated the effect of the GnRH antagonist cetorelix, administered with or without the GnRHa triptorelin, on oestradiol, LH and FSH levels [58]. The ovaries of these rats were also histologically studied and the number of follicles was counted [58]. This study found that triptorelin alone caused an initial increase in oestradiol on day 3 post administration [58]. This did not occur in the GnRH antagonist group or in the combination group where triptorelin was combined with cetorelix [58]. Treatment with triptorelin or cetorelix or a combination of both all reduced primordial follicle destruction [58].

A prospective study investigated 18 female patients who received the GnRH antagonist cetorelix in combination with the GnRHa goserelin and chemotherapy [59]. Nine patients were lost to follow-up, seven patients had lymphoma, one patient had breast cancer and one patient had Wegners granulomatosis [59]. Eight of the nine patients evaluated regained menses, normal levels of gonadotropins and detectable levels of oestradiol within 11 months after the completion of chemotherapy [59]. Two of the nine patients had successful pregnancies, with one of these patients conceiving spontaneously [59]. A pilot study evaluated the effect of GnRH antagonist, cetorelix, on ovarian function, in 18 women receiving cyclophosphamide chemotherapy [60]. The primary endpoint was resumption of regular menstrual cycles and serum FSH levels at 6 and 12 months after chemotherapy. Women received three doses of cetorelix over 12 days (one dose injected every four days), commencing 1 to 4 days before the onset of each chemotherapy cycle. At 12 months after chemotherapy, 14 of 15 evaluable women (94%)

had resumed regular menses [60]. Similarly, 14 of 15 (94%) women had normal levels of serum FSH at 12 months after chemotherapy (mean FSH 6.28 IU/L; range, 3.8–15 IU/L) [60].

Clinical evidence for efficacy of GnRHa treatment

Breast cancer studies

The majority of high-quality evidence for the efficacy of GnRHa in the prevention of COF comes from studies of premenopausal patients with breast cancer (Table 1).

An individual patient data meta-analysis, published in 2018 by Lambertini et al., included data from five randomised controlled trials, which examined the efficacy of GnRHa in preventing COF in premenopausal women receiving treatment for early-stage breast cancer. The studies included in this meta-analysis comprised trials that included either women with oestrogen receptor-positive breast cancer or women with oestrogen receptor-negative breast cancer, or both. It concluded that concurrent GnRHa (goserelin or triptorelin) administration resulted in a reduced risk of developing COF (adjusted odds ratio [OR] = 0.38; 95% CI = 0.26–0.57; $p < 0.001$) [61]. There was a lower rate of amenorrhoea at 2 years in patients treated with GnRHa compared to patients who were not (18.2% compared to 30.0%; adjusted OR = 0.51; 95% CI = 0.31–0.85, $p = 0.009$) [61]. Although menstruation does not always equate to fertility, there were more pregnancies in patients who received GnRHa concurrently with their chemotherapy (incidence rate ratio [IRR] = 1.83; 95% CI = 1.06–3.15, $p = 0.030$) [61]. All pregnancies occurred in patients who were under the age of 40 years at the time of their breast cancer diagnosis. Reassuringly, there were no significant differences in 5-year disease free survival (adjusted HR = 1.01; 95% CI = 0.72–1.42, $p = 0.999$) or 5-year overall survival (adjusted HR = 0.67, 95% CI = 0.42–1.06, $p = 0.083$) between women who received GnRHa and women who did not [61].

The three largest randomised controlled trials included in the meta-analysis were the Prevention of Early Menopause Study (POEMS), Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer – Gruppo Italiano Mammella 6 (PROMISE-GIM6) and Ovarian Protection Trial In Premenopausal Breast Cancer Patients (OPTION) trials. The POEMS open-label trial recruited premenopausal women aged 18–49 years with oestrogen receptor-negative breast cancer and randomised them to receive either the GnRHa goserelin or no GnRHa, concurrent with their curative-intent alkylating chemotherapy. In the intervention arm, goserelin 3.6 mg was injected subcutaneously at least 1 week before the commencement of chemotherapy and every 4 weeks during chemotherapy. The primary endpoint was assessed at 2 years and defined as the absence of menses in the preceding 6 months and FSH levels in the postmenopausal range. Only 8% of the GnRHa arm experienced COF at 2 years after chemotherapy compared with 22% of those randomised to receive chemotherapy without goserelin (OR = 0.30, 95% CI = 0.09–0.97; one-sided $P = 0.02$, two-sided $P = 0.04$) [42]. More patients in the GnRHa-treated group achieved pregnancies than those who were not (22 of 105, 21%, versus 12 of 113 patients, 11%; OR = 2.45, 95% CI = 1.09–5.51; $P = 0.03$) [42].

The PROMISE-GIM6 open-label trial of women with breast cancer (either oestrogen receptor positive or negative) randomised to receive either curative-intent chemotherapy alone or concurrent with the GnRHa triptorelin, also showed efficacy of GnRHa for the prevention of COF. The primary endpoint was defined as amenorrhoea and FSH and oestradiol levels in the post-menopausal range at 1 year after the end of chemotherapy [49]. In the intervention arm, triptorelin 3.75 mg was injected intramuscularly at least 1 week before the commencement of chemotherapy and every 4 weeks during chemotherapy [41]. The initial analysis showed a reduction in COF with the GnRHa, from 25.9% to 8.9% (OR = 0.28, 95% CI = 0.14–0.59; $P < .001$) [49]. After a median follow-up of 7.3 years, this effect was still observed. The 5-year cumulative incidence estimate of menstrual resumption in the group that received triptorelin was 72.6% (95% CI = 65.7%–80.3%) compared with 64.0% (95% CI 56.2%–72.8%) in the group that did not receive triptorelin (HR = 1.28, 95% CI = 0.98–1.68; $P = .07$) [41]. The 5-year cumulative incidence estimate of pregnancy was not statistically different; 2.1% (95% CI = 0.7%–6.3%) in the GnRHa group compared to 1.6% (95% CI = 0.4%–6.2%) in the group that did not receive GnRHa (HR = 2.56, 95% CI = 0.68%–9.6%, $p = 0.20$) [41].

Table 1
Randomised controlled trials investigating GnRH agonists for the prevention of COF in women with breast cancer.

Study	No. of patients ^a	HR ^b positive	HR negative	Primary endpoint	Primary endpoint: GnRH _a	Primary endpoint: No GnRH _a	P value	Pregnancy: GnRH _a	Pregnancy: No GnRH _a
Leonard et al., 2017 [43] OPTION	221	Yes	Yes	Amenorrhoea and post-menopausal FSH at 12–24 months	18.5%	34.8%	0.015	9%	6%
Moore et al., 2015 [42] POEMS	257	No	Yes	Amenorrhoea for the prior 6 months and post-menopausal FSH at 24 months	8%	22%	0.04	21%	11%
Lambertini et al., 2015 [41] PROMISE GIM6	281	Yes	Yes	Amenorrhoea and post-menopausal hormone levels for a 12-month interval	27.4%	36.0%	0.07	5%	2%
Song et al., 2013 [62]	220	Yes	Yes	Amenorrhoea and post-menopausal hormone levels	16.9%	28.7%	<0.01	NI	NI
Elgindy et al., 2013 [63]	100	No	Yes	Resumption of regular menses – three consecutive menses within 21–35 days each	80%	80%	1.00	8%	4%
Munster et al., 2012 [64]	49	Yes	Yes	Resumption of regular menses – three menses in a 6-month interval	88%	90%	0.36	0%	10%
Gerber et al., 2011 [65] ZORO	61	No	Yes	Resumption of regular menses – two menstrual periods within 21–35 days in 5–8 months	70.0%	56.7%	0.28	3%	3%
Badawy et al., 2009 [66]	80	NI ^c	NI	Resumption of regular menses and ovulation	89.6%	33.3%	<0.001	NI	NI

^a Number of patients randomised.

^b Hormone receptor.

^c Not investigated.

OPTION, published in 2017, recruited women with early-stage breast cancer, and these women were randomised to receive goserelin or nothing concurrently with adjuvant or neoadjuvant chemotherapy. Women with oestrogen receptor-negative breast cancer and women with oestrogen receptor-positive breast cancer, whom the investigators deemed as not requiring ovarian suppression as part of their treatment, were included in this trial. The primary endpoint was defined as no menses for 12–24 months after randomisation and elevated FSH [43]. Two hundred two of the 227 patients were evaluated. The rate of COF was 34.8% in the control arm versus 18.5% in the GnRHa arm ($P = 0.048$) [43]. In a pre-planned subgroup analysis, this benefit was most prominent in patients aged under 40 years, where the incidence of COF was 2.6% in the GnRHa arm versus 20.0% in the control arm ($P = 0.038$) [43]. The benefit of GnRHa was not statistically significant in women aged more than 40 years with a COF rate of 42.3% in the GnRHa arm compared to 47.2% ($p = 0.798$) [43].

GnRHa prescribing considerations

GnRHa is available as one-monthly and three-monthly formulations, but differences in their efficacy have not been directly compared. The one-monthly formulation has been used predominantly in the most recent randomised controlled trials [41–43].

The first dose of GnRHa should ideally be administered at least 1 week before alkylating treatment commencement, as there is an initial surge in FSH with the first dose of GnRHa, which is followed by the suppression of FSH [46]. This is not always possible, as unwell patients may need urgent treatment at the time of diagnosis. GnRHa should be started as soon as possible in these patients. Goserelin 3.6 mg is delivered via a depot subcutaneous injection, whereas triptorelin 3.75 mg is delivered as an intramuscular injection every 4 weeks during chemotherapy treatment. Appropriate training of staff administering the injection is important.

The potential side effects of GnRHa include vasomotor symptoms, headaches, sleep disturbance, depression, hot flushes, decreased libido and vaginal dryness [42,49]. The prevalence of these side effects is higher with concurrent use of GnRHa than with chemotherapy alone; however, most side effects are only of mild to moderate severity [42,49]. In the first month of treatment, some women experience vaginal bleeding of variable duration and intensity because of oestrogen withdrawal, but GnRHa should cause amenorrhoea following this. Despite amenorrhoea, information about non-hormonal contraception whilst on chemotherapy is important for all patients, as pregnancies can still rarely occur in women on goserelin and are highly undesirable during chemotherapy.

Women who have not yet completed their families should also be promptly referred to a fertility specialist. Counselling and subsequent cryopreservation for fertility preservation should occur in conjunction with the use of GnRHa in these women.

Summary

Ovarian failure can be a devastating consequence of alkylating chemotherapy. It can leave long-lasting effects after treatment cessation and impair quality of life. The avoidance of health issues associated with COF is an important consideration from not only an individual basis but also a public health perspective.

For the subgroup of women who have not completed their families before alkylating chemotherapy is to be initiated, it is very important to also consider specific fertility preservation options, including cryopreservation of embryos or oocytes or ovarian tissue. These methods do not prevent COF, and GnRHa should be considered in conjunction with cryopreservation in these women. For the subgroup of women who have completed their families, prevention of COF is vital for preventing the long-term health sequelae of early menopause.

Although the mechanism of action by which GnRHa protect ovarian function is imperfectly understood in patients with breast cancer treated with alkylating agents, there is an increasing body of evidence that administration of GnRHa starting at least 1 week before chemotherapy and then continuing throughout chemotherapy can substantially reduce the risk of COF. With the ready availability of GnRHa, discussion regarding ovarian function preservation will become an increasingly

important issue to address and will form an important part in improving survivorship for many young women diagnosed with cancer.

Practice points

- Chemotherapy-associated ovarian failure (COF) can be a devastating consequence of alkylating chemotherapy, commonly used in the curative-intent treatment for breast cancer.
- Treatment for reproductive cancers other than breast cancer often includes platinum-based chemotherapy. This has been shown in small studies to also affect ovarian function.
- COF can cause infertility, cognitive impairment, increased risk of fractures from reduced bone mineral density, increased risk for cardiovascular disease and reduction in quality of life.
- Cryopreservation of embryos or oocytes or ovarian tissue, although effective for fertility preservation, do not prevent COF.
- GnRHa treatment starting at least 1 week before chemotherapy and then continuing throughout chemotherapy can substantially reduce the risk of COF.
- Limited evidence is available for the efficacy of GnRH antagonists for the prevention of COF.
- GnRHa should be considered in all premenopausal women undergoing curative intent alkylating chemotherapy.

Research agenda

- The efficacy of GnRHa for the prevention of COF in women receiving non-alkylating chemotherapy such as platinum- and taxane-based chemotherapy.
- Identifying women who are most likely to benefit from GnRHa (clinical or biochemical).
- Long-term morbidity outcomes in women who received GnRHa compared to those who did not.
- The role of GnRH antagonist alone or in combination with GnRHa, especially in patients who require urgent chemotherapy that cannot be delayed to avoid the initial surge in FSH.
- Incorporation of measures of ovarian function as a standard in Phase III studies of new chemotherapy regimens.

Conflicts of interest

The authors have no conflicts of interest.

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