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Maximizing ovarian function and fertility following chemotherapy in premenopausal patients: Is there a role for ovarian suppression?

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ABSTRACT

As more premenopausal patients undergo fertility preserving cancer treatments, there is an increased need for fertility counseling and ovarian sparing strategies. Many patients receive gonadotoxic chemotherapeutic agents which can put them at risk of primary ovarian insufficiency or profoundly diminished ovarian reserve. Traditionally, estradiol and follicle stimulating hormone (FSH) values have been used to evaluate ovarian function but more recently, reproductive endocrinologists have been proponents of anti-mullerian hormone (AMH) as a validated measure of ovarian potential. While the gold standard for fertility preservation remains oocyte cryopreservation, data suggest there may be additional interventions that can mitigate the gonadotoxic effects of chemotherapeutic agents. The main objectives of this focused review were to quantify the risk of primary ovarian failure associated with the most common chemotherapies used in treatment of gynecologic cancers and to evaluate and recommend potential interventions to mitigate toxic effects on ovarian function. Chemotherapeutic agents can cause direct loss of oocytes and primordial follicles as well as stromal and vascular atrophy and the extent is dependent upon mechanism of action and age of the patient. The risk of ovarian failure is the highest with alkylating agents (42.2 %), anthracyclines (<10–34 % in patients under 40 years versus 98 % in patients aged 40–49), taxanes (57.1 %) and platinum agents (50 %). Multiple trials demonstrate that gonadotropin releasing hormone (GnRH) agonists, when administered concurrently with chemotherapy, may have protective effects, with more patients experiencing resumption of a regular menstruation pattern and recovering ovarian function more quickly post-treatment. Premenopausal patients receiving chemotherapy for the treatment of gynecologic cancers should receive adequate counseling on the potential adverse effects on their fertility. Although oocyte cryopreservation remains the gold standard for fertility preservation, there is some evidence to suggest that GNRH agonists could help maintain and preserve ovarian function and should be considered.

1. Introduction

Patients with gynecologic cancer should receive comprehensive counseling about adverse effects of chemotherapy on ovarian function, as well as options for preserving fertility and minimizing damage to the ovaries. As cancer treatment evolves and long-term survival improves, an increasing number of premenopausal patients are expected to experience the adverse effects of cancer treatment on fertility and ovarian function. In 2024, approximately 117,000 individuals are expected to be diagnosed with gynecologic cancers; while the minority will be premenopausal, for those patients who retain their ovaries and require chemotherapy, maximizing both fertility potential and minimizing loss

Abbreviations: POI, Primary ovarian insufficiency; POF, Premature ovarian failure; AMH, Anti-mullerian hormone; IVF, In-vitro fertilization; DNA, Deoxyribonucleic acids; FSH, Follicle stimulating hormone; LH, Luteinizing hormone; E2, Estradiol; GnRH, Gonadotropin releasing hormone; GnRHa, Gonadotropin releasing hormone agonists; BEP, Bleomycin, etoposide, platinum agent; ABVD, Doxorubicin, bleomycin, vinblastine, dacarbazine; GTN, Gestational trophoblastic disease; M-EA, Methotrexate and actinomycin; EMA-CO, Etoposide, methotrexate, Actinomycin-D with cyclophosphamide, vincristine; ART, Assisted reproductive technology; PARPi, Poly-ADP-ribose polymerase inhibitors; VEGF, Vascular endothelial growth factor; HER2, Human epithelial receptor 2; REI, Reproductive Endocrinology and Infertility; COCs, Combined oral contraceptive pills.

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of ovarian function are of paramount importance (Siegel et al., 2024). Premature loss of ovarian function, whether due to surgery or chemotherapy, is associated with increased morbidity and mortality due to cardiac disease, osteoporosis and dementia (Wu et al., 2022). Studies have demonstrated that cancer survivors are more concerned about their fertility potential than healthy patients ($p < 0.0001$) yet a majority are not undergoing fertility counseling or preservation and data are lacking regarding counseling on the non-fertility impact of chemotherapy on ovarian function (Gershenson et al., 2007). Many chemotherapeutic agents have known gonadotoxic effects, including platinum and alkylating agents, but many agents have relatively unknown effects and this is especially true of newer targeted therapies and immunotherapies. In addition, there is relative paucity of fertility preservation literature in gynecologic oncology patients as most of the existing data are derived from patients with lymphomas, leukemia and breast cancer (Meirow, 2000).

The heterogeneity of key outcome measures and assessment of fertility in existing studies makes it difficult to counsel patients about the effects of specific treatment regimens on their future fertility and ovarian function. The key outcome measure for some studies is resumption of menstruation which is an indicator of primary ovarian insufficiency (POI) that identifies only the most severe cases of gonadal toxicity. While studies have assessed ovarian reserve, many utilized FSH as an endpoint, which is elevated only in the setting of profound diminished ovarian reserve and may be normal in patients who have suffered significant gonadal damage from treatment. While more recent studies have evaluated anti-mullerian hormone levels (AMH), a convenient and reliable means of determining ovarian reserve, AMH is not a reliable predictor of future fertility, but rather is a marker for favorable response to fertility treatment in patients who require it (Steiner et al., 2017). Predicting future fertility based on ovarian reserve testing, except in patients who experience POI, is generally not possible. In young women, however, diminished ovarian reserve following gonadotoxic therapy should be viewed as a significant adverse effect. Diminished ovarian reserve increases the risk of future POI or early menopause which may occur prior to completion of childbearing (Freeman et al., 2012). For those patients with infertility, diminished ovarian reserve dramatically decreases the efficacy of *in vitro fertilization* (IVF), the most effective fertility treatment (Anckaert et al., 2012).

It is therefore essential to identify cancer patients at high risk of chemotherapy-induced oocyte loss in order to facilitate fertility preservation as well as maximize long term ovarian function for overall health and well-being. The objectives of this review are to outline the most current data on the impact on ovarian function for each of the most commonly used chemotherapeutic agents in the treatment of gynecologic cancers, to evaluate the data on potential interventions to mitigate adverse ovarian outcomes and retain fertility options, and to make recommendations for best practices when treating premenopausal women who retain their ovaries to limit the adverse reproductive and endocrinological effects of chemotherapy.

2. What are the mechanisms for ovarian toxicity of the common chemotherapy regimens used in gynecologic oncology?

2.1. Pathophysiology of chemotherapy induced gonadotoxicity

(1) Diminished ovarian reserve

Chemotherapeutic agents have a significant deleterious effect on ovarian function and cause loss of oocytes (Meirow, 2000; Blumenfeld, 2012). The primary mechanism causing loss of primordial and primary follicles during chemotherapy is presumed to be via cellular apoptosis which most likely occurs as a response to irreparable double stranded DNA breaks. A study utilizing human xenograft ovarian tissue models exposed to cyclophosphamide demonstrated a significant loss of primary follicles, as evidenced by the presence of apoptotic enzymes, within 12 h of exposure to cyclophosphamide (Bedoschi et al., 2016). This irreparable damage then depletes a patient's follicular reserve, and, if significant enough, patients experience premature ovarian failure (Bedoschi et al., 2016).

Cancer survivors may be either permanently or temporarily amenorrheic and can exhibit all the symptoms of menopause and POI. While POI is the worst possible result of chemotherapy-induced loss of oocytes, it is important to view the effects of chemotherapy-induced gonadotoxicity as a continuum. Patients with mild or moderate diminished ovarian reserve may have normal menses, normal FSH, and may demonstrate no discernable symptoms of gonadotoxicity, but may experience these sequelae later in life. The adverse effects of diminished ovarian reserve range from early onset of menopause, inability to successfully preserve fertility through oocyte or embryo cryopreservation, and inability to successfully undergo fertility treatments such as IVF.

(2) Adverse impact on ovarian stroma and vasculature

In addition to directly impacting ovarian follicles, chemotherapeutic agents also affect ovarian stroma and vasculature which indirectly affects fertility and function. *In vivo* studies showed a dose-dependent decrease in blood vessel density in ovarian stromal cells cultured with saline vs doxorubicin (Bedoschi et al., 2016). Murine studies have shown that taxanes, doxorubicin, and cisplatin exposure cause disordered ovarian stroma and evidence of ovarian atrophy (Zhang et al., 2023). Treatment of ovarian stroma, specifically granulosa cells, with these same agents causes mitochondrial dysfunction due to the presence of reactive oxygen species which induces cell apoptosis (Zhang et al., 2023; Ben-Aharon and Shalgi, 2012). This can lead to poor vascularization and stromal fibrosis which, in turn, can diminish ovarian hormonal function and follicular reserve.

2.2. Rationale for use of GnRH agonists in the prevention of chemotherapy induced toxicity

Uncertainty still exists over the efficacy of ovarian suppression during chemotherapy in protecting future fertility and ovarian function. The current ASCO guidelines simply state that they can be used based on the limited evidence supporting the efficacy of gonadotropin releasing hormone agonists (GnRHa) in preserving ovarian function during chemotherapy. Gonadotropin releasing hormone (GnRH) stimulates the release of gonadotropins which trigger the growth of granulosa cells (Poggio et al., 2019). GnRHa, through gonadotropin downregulation, cause ovarian follicles to enter a quiescent phase, theoretically decreasing their exposure to chemotherapy (Poggio et al., 2019). Other theories include protection from gonadotoxic agents due to a decrease in ovarian perfusion secondary to estrogen downregulation, upregulation of antiapoptotic enzymes like sphingosine-1-phosphate and direct activation of GNRH ovarian receptors which may prevent apoptosis (Poggio et al., 2019; Blumenfeld, 2007; Kitajima et al., 2006). Within the ovary, follicles are responsible for the growth and maturation of an oocyte with each ovulation event. FSH, LH, and GnRH receptors do not exist within primordial follicles, meaning that GnRH agonists and antagonists do not have a direct effect on ovarian reserve. In a randomized trial studying the effects of cyclophosphamide on mouse ovarian tissue, there was no difference in rates of apoptosis, follicular loss, or cell proliferation for mice receiving GnRHa (Horicks et al., 2018). In an *in vitro* model using ovarian cortical pieces and human granulosa cells, tissue was exposed to a variety of chemotherapeutic agents with or without a GnRHa. Administration of a GnRHa was not found to activate any anti-apoptotic pathways or prevent massive follicular loss in these models (Bildik et al., 2015). Despite this, data indicate that women who received GnRHa prior/during chemotherapy are more likely to have menses resume following treatment. To date, however, there is little evidence to show that these agents are efficacious in preserving fertility.

2.3. Agent specific ovarian effects (Table 1, Fig. 1)

Chemotherapeutic agents differ in their effects on ovarian function and patient specific factors, especially age, also play a role. Meirow et al found that older patients (34 years of age and older), had a statistically significant increased risk of decreased ovarian function defined as amenorrhea or FSH/LH levels > 15 IU/L for at least 6 months after completion of treatment as compared to younger patients (27 years of age and younger) (Meirow, 2000). Additionally, baseline ovarian reserve and duration of treatment can contribute to a patient's fertility outcome, however, the multifactorial aspect and lack of precise prognostic information makes it difficult for clinicians to provide specific information on the magnitude of potential gonadotoxic effects) (Meirow, 2000).

2.3.1. Alkylating agents

Alkylating agents interrupt DNA replication and cell division by creating bonds between DNA strands which can affect both proliferating cells and cells at rest (Blumenfeld, 2007). There is evidence that cyclophosphamide induces oxidative stress causing toxic effects on the granulosa cells surrounding mature follicles (Chang et al., 1993). In addition, there are data indicating that cyclophosphamide has a dose dependent toxic effect on ovarian follicles, and older patients tend to develop amenorrhea at a lower dose than younger patients (Fleischer et al., 2011; Koyama et al., 1977). Meirow et al found that patients treated with alkylating agents had a significantly higher rate of ovarian failure compared to other chemotherapy agents (42.4 % vs. 14 %; $p < 0.001$) (Meirow, 2000).

2.3.2. Anthracycline antibiotics

Doxorubicin induces double stranded DNA breaks leading to p63-mediated cellular induced apoptosis and there are limited human studies evaluating fertility (Bedoschi et al., 2016). Rates of amenorrhea after doxorubicin appear to vary drastically with age, with women aged 40–49 experiencing a 96 % amenorrhea rate compared to younger patients with rates ranging from under 10 % to 34 % (Ben-Aharon and Shalgi, 2012). In Hodgkin's lymphoma patients treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), retrospective studies found no statistical difference in fertility rates in patients compared to controls (Hodgson et al., 2007; Machet et al., 2023). One mouse study showed significant and progressively decreasing ovulation rates following intraperitoneal injections of doxorubicin (100 % ovulation rate in controls, 50 % ovulation in doxorubicin treated mice at 48 h and 4 % ovulation rate at one week and then a 52 % rate at one month) (Ben-Aharon et al., 2010). Another study cultured mouse ovarian follicles with doxorubicin for 24 h and analyzed hormone secretion, follicle development and oocyte maturation and showed a dose dependent effect for follicle survival with a survival rate (90 % vs 50 % as compared to controls by day 2 for follicles treated with 100 nM and 200 nM of doxorubicin) (Xiao et al., 2017).

2.3.3. Taxanes

Taxanes alter several cellular processes, mainly the microtubule assembly mechanism, ultimately leading to cell cycle arrest (Wu et al., 2022). A meta-analysis of premenopausal early-stage breast cancer patients (age < 46) being treated with anthracycline/taxane therapy found that 85 % met criteria for ovarian failure at the end of treatment and 32.6 % still met criteria at two years as defined by FSH levels > 12.4 IU/L and estradiol levels < 52.2 ng/L (Furlanetto et al., 2021). Approximately 72.4 % of patients who did not meet criteria for ovarian failure also had low AMH levels, which indicates some level of ovarian dysfunction. Of the patients treated only with paclitaxel, the chemotherapy induced ovarian failure was 57.1 % at end of treatment and 25 % at two years (Furlanetto et al., 2021). Another separate study of breast cancer patients demonstrated a 15 % rate of long-term amenorrhea (Fornier et al., 2005).

2.3.4. Platinum agents

These crosslinking heavy metal agents prevent DNA transcription, replication and function which ultimately triggers the apoptotic cellular death pathway (Bedoschi et al., 2016; Kelland, 2007). In one study, 50 % of patients treated with cisplatin and bleomycin became amenorrheic within 10 weeks after receiving only 1–2 doses (Maneschi et al., 1994). Meirow et al looked at reproduction post-treatment in patients with leukemia, non-Hodgkin's lymphoma, and bone marrow transplant, and did not find a significant increased risk of ovarian failure in patients treated with *cis*-platinum agents, although the study may have lacked sufficient power (Meirow, 2000).

2.3.5. Bleomycin, Etoposide, Platinum (BEP) and other platinum based combinations

Bleomycin induces double strand DNA breaks and is commonly used alongside etoposide and platinum agents (BEP) in the treatment of ovarian germ and sex-cord stromal cell tumors. Etoposide is an antineoplastic agent that induces cellular apoptosis by inhibiting topoisomerase II and creating double strand DNA breaks (Hande, 1998). Unfortunately, there are little human single agent data on ovarian toxicity. One mouse study showed no statistically significant difference between AMH levels of mice injected with bleomycin compared to controls but did show higher follicle counts in mice treated with bleomycin and either triptorelin or ceterolix (GnRH agonist and antagonist respectfully) as compared to bleomycin alone ($p < 0.001$) (Atakul et al., 2021). One Korean study looked at the reproductive and fertility outcomes in 15 patients diagnosed with malignant ovarian germ cell tumors

Table 1
Common chemotherapy and immunotherapy agents and their effect on ovarian function.

Chemotherapy agent	Antineoplastic mechanism	Risk of ovarian failure	Resumption of Ovarian Function	Pregnancy rate after treatment
Alkylating agents	Inhibit DNA replication	42.2 % after treatment	unknown	No data
Platinum agents	Cross link DNA strands and inhibit replication and transcription	50 % (with bleomycin), OR of 1.77	unknown	unknown
Taxanes	Microtubule instability	57.1 % at 12 months	75 % at 24 months	unknown
Anthracyclines	Double strand DNA breaks leading to apoptosis	85 % at end of treatment (when combined with paclitaxel) 98 % (40–49 years) <10–34 % (<40 years)	67.4 % by 24 months	Data limited to murine models
Antimetabolites (methotrexate)	Inhibits dihydrofolate reductase causing T cell apoptosis	unknown	60 % with normal menses	46–57.1 %
BEP	Combination therapy	7 % after treatment	94–100 % with normal menses	95 %
EMA-CO	Combination therapy	unknown	unknown	36.4–56 %
Trastuzumab	Inhibits growth/signaling of HER2+ cells	28 % with long term amenorrhea	Evidence for protective effects	none

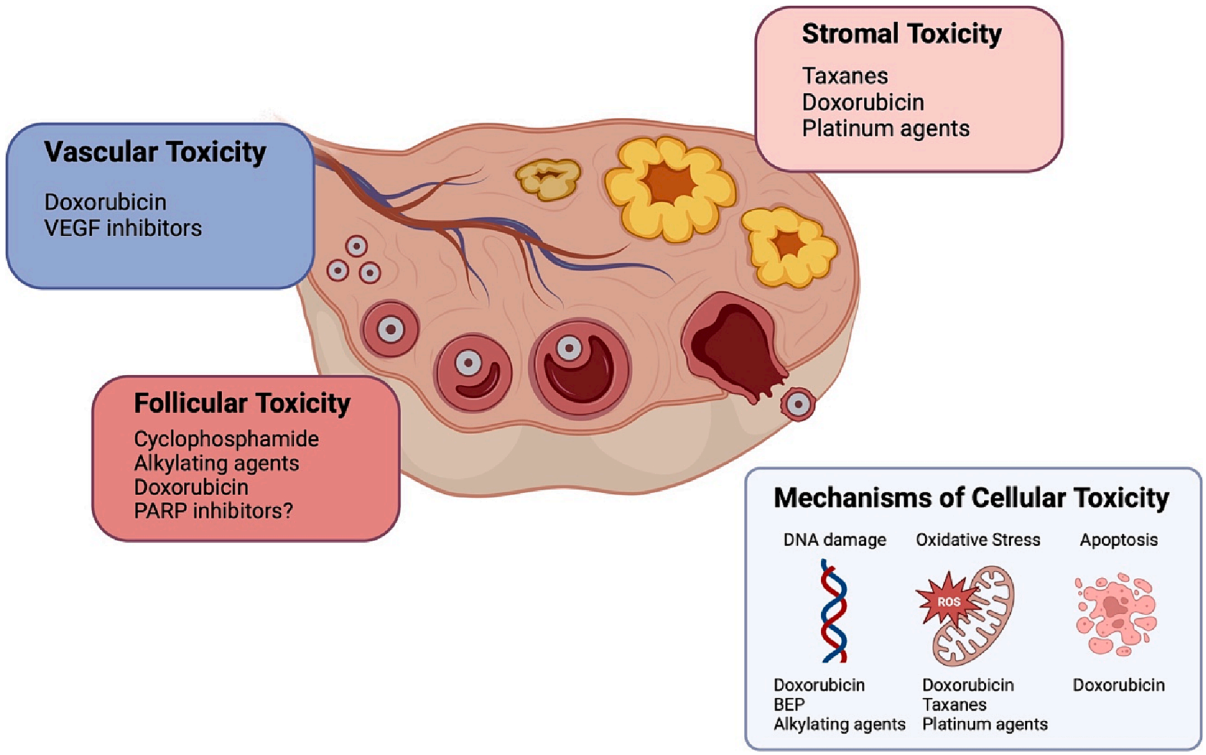

Fig. 1. Location and mechanisms of gonadotoxic effects of various chemotherapeutic agents.

following BEP treatment noted that 100 % resumed menses after completing BEP treatment and two patients went on to have successful pregnancies (Kang et al., 2008). Brewer et al noted that 94 % (13/14) of their patients with ovarian dysgerminomas treated with BEP therapy experienced resumption of their prechemotherapy menstrual pattern after treatment, five of whom (35 %) continued to have a normal menstrual pattern throughout treatment (Brewer et al., 1999). Another study reported a 95 % conception rate among those patients who attempted to conceive (n = 20) after completing BEP treatment, and of the 16 live births that were reported, 14 were from the chemotherapy group (Low et al., 2000).

In 2023, a retrospective study evaluated fertility outcomes, specifically pregnancies, after treatment with BEP or paclitaxel/cisplatin for malignant ovarian germ cell tumors in 213 patients (Chu et al., 2023). Of the 51 total patients who desired pregnancy, 43 (84 %) achieved a pregnancy, 40 naturally and with 35 successful deliveries; there were no significant differences in fertility outcomes between the two groups (Chu et al., 2023). Similarly, a Thailand study of 110 women under 40 treated for malignant ovarian germ cell tumors (mainly BEP but also including cisplatin/vincristine/actinomycin D/cyclophosphamide, cisplatin/vinblastine/bleomycin and vincristine/actinomycin D/cyclophosphamide) found 79.2 % experienced menstrual recovery with a median time to recovery of 6 months (Tamauchi et al., 2018). The vast majority of patients who desired pregnancy, (42/45, 93.3 %) became pregnant and only 7 patients required assisted reproductive technology; eight patients with successful deliveries had FIGO stage II to III disease and the authors concluded that advanced stage disease does not preclude consideration of fertility preservation (Tamauchi et al., 2018).

2.3.6. Antimetabolites and combinations including them Etoposide, methotrexate, Actinomycin-D with cyclophosphamide and vincristine (EMA-CO)

Antimetabolites target cell metabolism by inhibiting enzymes involved in nucleotide base synthesis and includes agents like gemcitabine, 5 FU, capecitabine, and methotrexate. It is thought that because antimetabolites are cell cycle specific, they are less likely to affect primordial follicles and therefore have less of a gonadotoxic effect (Ajala et al., 2010). A retrospective analysis of patients with gestational trophoblastic disease (GTN) who were treated with either M-EA (methotrexate and actinomycin) vs EMA-CO (etoposide, methotrexate, Actinomycin-D with cyclophosphamide and vincristine) found that 46 % of patients in the M-EA group became pregnant (with 26 deliveries and 1 miscarriage) and 35 % in the EMA-CO group (6 deliveries and 1 miscarriage) (Singh et al., 2021). Another study found that 60 % of patients (n = 15) had regular menstrual cycles between 6 and 18 months after completing M-EA treatment and 45.5 % (n = 5/11) of those who desired were able to bear children (Sato et al., 2020). The authors hypothesized that fertility rates may be worse after treatment with EMA-CO vs M-EA due to the inclusion of cyclophosphamide (Sato et al., 2020).

In 1979, etoposide was incorporated into a preexisting regimen for the treatment of gestational trophoblastic neoplasia (GTN), creating the EMA-CO regimen. In China between 1979 and 1995, this regimen was used to treat 272 patients with high risk GTN, a majority of whom (n = 121) had already received prior chemotherapy treatments (Bower et al., 1997). At five years, the cumulative overall survival rate was 86.2 % (95 % CI, 81.9–90.5 %), and at two years after treatment, 56 % (n = 152) had successfully become pregnant (Bower et al., 1997). One study compared fertility outcomes in patients with GTN treated with single vs multiple agent regimens and found a higher pregnancy rates, albeit not statistically significant (57.1 % vs. 36.4 %; p = 0.06) and no difference in miscarriage rate or premature birth rates (Cioffi et al., 2018). Further, this study reported that only age and desire for pregnancy statistically impacted either group's probability of a subsequent pregnancy (p = 0.006 and p = 0.002 respectively) even when chemotherapy regimen and use of ART (assisted reproductive technology) were included in the analysis (Cioffi et al., 2018).

2.4. New targeted agents

Treatments for gynecologic cancers continue to improve and targeted agents, antibody drug conjugates and immunotherapies have now

become standard of care for the treatment of many gynecologic cancers. Unfortunately, the potential ovarian toxicity associated with these new targeted agents remains unclear. Given that many of these agents are third or fourth line therapies, few pateints who are receiving these therapies will be eligible for fertility sparing treatment. However, for those who do retain their ovaries, they will still be susceptible to agent-specific negative ovarian effects and may benefit from the following information.

2.4.1. PARP inhibitors

Poly-ADP-ribose polymerase inhibitors (PARPi) prevent part of DNA damage response and are important for the maintenance of genetic stability (Li et al., 2023). Despite the increase in clinical use of PARPi, little is understood about the effects on ovarian reserve. Theoretically, impairment of DNA repair processes could cause follicular and granulosa cell death which could further deplete a patient's ovarian reserve. Olaparib, a PARP1/2 inhibitor, has been shown to deplete primordial follicle count and reduce retrievable oocytes during *in vitro* fertilization (IVF) studies in mice but that oocyte retrieval rates improved after cessation of treatment (Nakamura et al., 2020).

2.4.2. VEGF inhibitors

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF) receptors and development of antral follicles and maturation of dominant follicles requires an increase in vascular supply. Bovine and porcine models have demonstrated an increase in the expression of VEGF receptors during follicle development and studies involving non-human primates have shown that blocking VEGF receptors has resulted in transient interference of normal follicular development with later recovery of follicle numbers (Berisha et al., 2000; Zimmermann et al., 2001).

2.4.3. Trastuzumab

Trastuzumab is a humanized anti human epithelial receptor 2 (HER2) monoclonal antibody that may actually decrease the gonadotoxic effects of chemotherapy on ovarian tissue due to its effect on VEGF expression (Levi et al., 2020). In mouse studies, researchers noted higher AMH levels in those who received trastuzumab in addition to either cyclophosphamide or paclitaxel than in those who received chemotherapy alone ($p < 0.05$) (Levi et al., 2020). In the breast patients, they found more detectable AMH levels in the group receiving traztuzumab with cyclophosphamide (57.1 % vs. 36.8 %; $p < 0.05$) (Levi et al., 2020). Similar results have also been noted in breast cancer patients treated with adjuvant paclitaxel and trastuzumab with a 28 % (95 % CI 18–41 %) rate of long-term amenorrhea (median time of 4 years) in premenopausal women (median age 44) which is lower than than many other studies reporting amenorrhea rates of 50–55 % at 36 months (Ruddy et al., 2015; Bernhard et al., 2007). These data support the notion that trastuzumab may have a protective effect on ovarian reserve and emphasizes the need for further studies.

3. What workup/evaluation is needed to assess baseline ovarian/reproductive function and potentially predict the impact of treatment?

3.1. Assessment of baseline ovarian function

Ovarian function is conserved until the pool of primordial follicles that comprise a woman's ovarian reserve is nearly completely depleted, and women with profound diminished ovarian reserve may have no obvious signs or symptoms. Measuring ovarian reserve using AMH as a biomarker for the number of primordial follicles in the ovaries has now been validated. AMH, a hormone that is related to the TGF-beta family, is produced by the immature preantral and antral follicles and does not vary significantly during the course of a woman's ovulatory cycle and can be drawn without menstrual cycle timing (Dewailly et al., 2014). AMH will decrease before FSH rises and is a reliable predictor of response of oocyte yield in patients who are undergoing oocyte freezing (Practice Committee of the American Society for Reproductive Medicine, 2020). While other measures like FSH and estradiol have been used for ovarian assessment, AMH has largely replaced these as a marker for ovarian reserve.

FSH and estradiol (E2) levels have historically been utilized to diagnose POI (formerly referred to as premature ovarian failure), a disorder marked by the absence of menses (three to four months of amenorrhea), elevated FSH levels (typically greater than 30–40 IU/l) and low E2 (less than 50 pg/mL) in a patient under forty years of age. Although a rise in FSH during the early follicular phase of a woman's menstrual cycle is often observed in the setting of diminished ovarian reserve, this does not occur during each cycle, may be masked by a functional ovarian cyst or use of exogenous hormones (including combined hormonal contraceptives), and typically occurs in women with profoundly diminished ovarian reserve. Because of these limitations and the availability of AMH testing, testing FSH and E2 alone is a suboptimal practice when assessing gonadal toxicity following cancer treatment.

One limitation of using AMH to assess ovarian reserve in patients who have received treatment for cancer is that there are no established cut-off values for AMH to predict the progression to menopause and the development of vasomotor symptoms. Yet diminished ovarian reserve, even without infertility or POI, likely remains an adverse effect of receiving gonadotoxic therapy and there does seem to be an independent and significant association between lower AMH levels and early onset vasomotor symptoms such that some have proposed that the onset of menopause can be predicted using a patient's AMH and age (Nam-Goung et al., 2022; Broer et al., 2011). For any premenopausal patient who is planning to receive chemotherapy, and especially those who desire future fertility, an AMH level should be drawn before and after treatment to assist patients pursuing fertility treatments but also can also assist clinicians in counseling their patients on the long-term effects of their treatments.

4. What is the optimal strategy or intervention for premenopausal gynecologic oncology patients receiving chemotherapy to optimize both future fertility and ovarian function?

Patients who require chemotherapy should be told, unequivocally, that the most reliable means of preserving their fertility is through oocyte or embryo cryopreservation prior to initiating chemotherapy. Thus, every oncology patient who may be interested in future fertility for whom gonadotoxic therapy is planned should be offered an early referral to a Reproductive Endocrinology and Infertility (REI) specialist. Many clinics are willing to offer urgent appointments, and when appropriate, urgent treatment, and serve as dedicated collaborators with their colleagues in oncology. Oocyte or embryo cryopreservation typically takes less than three weeks and now can be completed independent of menstrual cycle timing (McClam and Xiao, 2022). Oocyte or embryo cryopreservation before chemotherapy does not cause an adverse impact with respect to progression free or overall-survival, and does not significantly delay initiation of chemotherapy (Arecco et al., 2020). Suppressive therapy should be considered a secondary option for patients who are unable to go through oocyte or embryo cryopreservation (Arecco et al., 2020), or as an adjunct to these treatments to prevent ovarian insufficiency.

4.1. Initial workup to assist with evaluation of fertility and ovarian function

To assist with appropriate counseling, consider obtaining a baseline pre-treatment AMH (with or without FSH/E2) if feasible. An AMH is the most objective predictor of success with assisted reproductive technology, and having this information at time of REI consultation will help

with proper planning for a patient interested in pursuing treatment. AMH is widely covered by most commercial insurances when billing under Fertility Testing with ICD-10 code Z31.41.

4.2. Ovarian suppression with GNRHa background and options (Table 2)

Ovarian suppression can be achieved by using gonadotropin-releasing hormone agonists (GnRHa) or combined oral contraceptive pills (COCs). Current American Society of Clinical Oncology guidelines (updated in 2018) currently states that "There is conflicting evidence to recommend gonadotrophin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency (Oktay et al., 2018)."

Multiple large studies have evaluated the use of GnRHa in ovarian suppression during chemotherapy to protect future fertility potential, however most have focused on patients with breast cancer (Table 2) (Del Mastro et al., 2011; Moore et al., 2015; Leonard et al., 2017; Park et al., 2014). A recent review on the efficacy of GnRHa use found that fewer than 20 % of women diagnosed with breast cancer before the age of 40 underwent oocyte or embryo cryopreservation, but more than 90 % agreed to suppressive therapy prior to and during treatment (Blondeaux et al., 2021). A Cochrane review in 2019 evaluated 12 randomized control trials and concluded there is evidence that menstrual recovery within the first 12 months after treatment is higher (74.5 % vs 50.0 %, $p = 0.006$) and premature ovarian failure is lower (10.7 % vs 25.3 %, $p < 0.00001$) when GNRH agonists are co-administered (Chen et al., 2019).

Several large breast cancer trials merit further mention. One multicenter non-inferiority Phase III trial evaluated 281 breast cancer patients receiving neoadjuvant/adjuvant chemotherapy (either anthracycline or cyclophosphamide, methotrexate, and fluorouracil) with or without triptorelin (a GNRHa) on early menopause after chemotherapy and reported a significantly higher rate of early menopause at one year in the chemotherapy alone arm (25.9 % vs. 8.9 %; $p < 0.001$) (Del Mastro et al., 2011). Another Phase III trial randomized 218 breast cancer patients to chemotherapy vs. chemotherapy and goserelin (GnRH agonist) treatment and found a significantly higher ovarian failure rate defined as absence of menses for 6 moonths and elevated FSH at in the chemotherapy alone group (22 % vs 8 %;$p = 0.04$) (Moore et al., 2015). In this trial, a minority of patients attempted pregnancy (18 % of chemotherapy group and 24 % of the goserelin group) and patients who achieved pregnancy were younger (32.9 vs. 39.6 years, $P < 0.001$) (Moore et al., 2015). The percentage of patients in this study who achieved pregnancy did not differ based on treatment group, however there were significantly more live births in the goserelin group compared to the chemotherapy-only group (22 vs. 12, odds ratio, 2.45; 95 % CI, 1.09–5.51; $P = 0.03$). The OPTION trial was a prospective, randomized study of 227 breast cancer patients randomized to either chemotherapy with goserelin or chemotherapy alone and found a decreased prevalence of amenorrhea between 12 and 24 months with addition of goserelin (22 % vs. 38 %; $P = 0.015$) (Leonard et al., 2017). In addition, study participants experienced decreased rates of POI (18.5 % for patients receiving goserelin, 34.8 % of control group; $P = 0.048$), defined as amenorrhea with FSH greater than or equal to 25 IU/L. The protective effect of goserelin was not seen for patients older than 40 years of age. Nine pregnancies occurred in the treatment group and six pregnancies in the control group, however it was not reported how many patients attempted pregnancy. In a follow up study, the quality of life of patients in the OPTION trial receiving goserelin was examined and patients in the GnRHa arm experienced higher levels of vasomotor symptoms during the treatment phase (Leonard et al., 2017).

Outside of breast cancer, data and trials are more limited. One prospective trial in 115 patients with Hodgkin Lymphoma receiving extensive multi-agent chemotherapy regimens with or without the addition of GnRHa evaluated the impact on. premature ovarian failure (POF). POF was defined as persistent amenorrhea with FSH > 40 U/L on at least two occasions and low E2 levels and the study also measured rates of cyclic ovarian function (considered normal), normal gonadotropins and E2 levels, ovulatory progesterone, and visualization of ovarian follicles or corpus luteum or spontaneous conception. The GNRHa group had tenfold lower rate of POF (3.1 % vs. 37 % of the control group; $p < 0.001$) but there was no difference in spontaneous pregnancy rate (Blumenfeld et al., 2008).

Studies involving ovarian suppression during treatment of gynecologic cancers have been small and largely retrospective. A Korean retrospective study evaluated 14 patients with cervical or ovarian cancer who received Leuprolide (GnRH agonist) with add-back therapy during chemotherapy treatment (BEP for ovarian and carboplatin or

Table 2
Summary of trials assessing the addition of GnRH agonists for ovarian protection.

Trial Name	Type of Study	Patients	Trial Arms (control vs study arm)	Primary Outcomes
Cochrane Review	Meta Analysis of 12 RCTs*	Hodgkin's lymphoma, breast or ovarian malignancy	Chemo alone (mostly alkylating or platinum agents) vs. Chemo + GnRHa	Menstrual recovery within 12 months: Chemo alone: 74.5 % Chemo + GnRHa: 50.0 %
PROMISE-GIM6	RCT* Phase III trial	Stage I-III breast cancer	Chemo alone (anthracycline, anthracycline plus taxane, or CMF**) vs. Chemo + triptorelin	Menopause rates: Chemo alone: 25.9 % Chemo + triptorelin: 8.9 %
POEMS	RCT* Phase III trial	Stage I-IIIA ER/PR negative breast cancer	Chemo alone (cyclophosphamide-containing regimen) vs. Chemo + goserelin	Ovarian failure rate (No menstruation for 6 months): Chemo alone: 22 % Chemo + goserelin: 8 %
OPTION	RCT*	Stage I-IIIB breast cancer	Chemo alone (cyclophosphamide and/or anthracycline ± taxane) vs. Chemo + goserelin	Amenorrhea between 12 and 24 months after treatment: Chemo alone: 38 % Chemo + goserelin: 22 % POI (amenorrhea + FSH > 25 IU/L): Chemo alone: 34.8 % Chemo + goserelin: 18.5 %
Korea study	Retrospective study	1B1/1B2 cervical and 1C1 ovarian cancer	BEP + GnRHa, CarboTaxol + GnRHA or carboplatin + GnRHA	FSH levels (with > 40 IU/L indicating POF): FSH < 40 IU/L: 92.9 % FSH > 40 IU/L: 7.1 %

* Randomized control trial.
** Cyclophosphamide, methotrexate, fluorouracil.

carboplatin/taxane for cervical) (Park et al., 2014). One patient in the GNRHa group experienced premature ovarian failure, defined as FSH > 40 IU/L and vasomotor symptoms. One patient became pregnant following chemotherapy, and the number of patients attempting pregnancy was not discussed. Another small RCT performed in Iran included 30 patients between 12 and 40 years of age and found 100 % vs 66 % (95 % CI 1.02–2.13) menstrual recovery rate within the first 12 months in ovarian cancer patients treated with diphereline (GNRHa) compared to those that weren't (Gilani et al., 2007).

The above trials suggest that suppressive therapy with GNRHa may reduce the chance of developing ovarian insufficiency after chemotherapy, but were not designed or powered to assess the effects of suppressive therapy on future fertility. Additionally, all have limitations due to their varying definitions of fertility outcomes, and due to use of markers not necessarily clinically relevant to fertility outcomes. While a standard of care has not been established, there does appear to be evidence to support use of GnRHa or OCPs for the purpose of preventing ovarian insufficiency after chemotherapy. These medications may also have a role in preventing unwanted side effects from chemotherapy such as heavy menstrual bleeding, and patients should be counseled on the safety of continuous menstrual suppression if desired.

5. Conclusions: Best practice recommendations

Fertility counseling, the risks and benefits menstrual suppression, and the potential detrimental gonadotoxic effects of certain chemotherapeutic agents, should be discussed with all premenopausal patients undergoing treatment of gynecologic cancers. Recent data support the use of AMH as a marker of ovarian reserve and the addition of this biomarker to any routine pre-treatment laboratory work should be considered. Concurrent REI referral for all patients prior to initiation of treatment should be offered and patients counseled about potential cryopreservation of oocytes or embryos as the most effective means of fertility preservation. While there is conflicting evidence about the effectiveness of ovarian suppression during chemotherapy, there appears to be no significant negative side effects of GNRH agonists, such as triptolerin and leuprolerin and there may be a potential benefit and should be discussed with patients as an option.

6. Future areas of exploration

The authors note that as of time of publication, there are a lack of large studies specifically looking at fertility preservation in patients with primary gynecologic cancer who may be much younger than their breast cancer counterparts. While the gonadotoxic effects of chemotherapy agents should not differ when administered to a patient with a gynecologic malignancy, these diseases may affect patient populations which vary in average age, time to diagnosis, and subjective fertility goals making this a research area worth further exploration.

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None of the authors have anything to disclose.

8. Consent statement

This was a literature review and therefore was exempted from the consent process.

CRediT authorship contribution statement

Kelsey A. Roof: Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Kerri E. Andre:** Writing – review & editing, Writing – original draft, Investigation. **Susan C. Modesitt:** Writing – review & editing, Supervision, Resources. **D. Austin Schirmer:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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