Cancer Treatment Reviews 72 (2019) 65–77

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

General and Supportive Care

Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: From biological evidence to clinical application

Matteo Lambertini[a,*,1], Florence Horicks[b,1], Lucia Del Mastro[c,d], Ann H. Partridge[e], Isabelle Demeestere[b]

[a] Department of Medical Oncology and Breast Cancer Translational Research Laboratory, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[b] Fertility Clinic, CUB-Hôpital Erasme and Research Laboratory on Human Reproduction, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[c] Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, Ospedale Policlinico San Martino-IST, Genova, Italy
[d] Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genova, Genova, Italy
[e] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

ARTICLE INFO

Keywords:
Premature ovarian insufficiency
Gonadotoxicity
Fertility
Young patients
GnRHa

ABSTRACT

Survivorship issues are an area of crucial importance to be addressed as early as possible by all health care providers dealing with cancer patients. In women diagnosed during their reproductive years, the possible occurrence of chemotherapy-induced premature ovarian insufficiency (POI) is of particular concern being associated with important menopause-related symptoms, psychosocial issues as well as infertility. Temporary ovarian suppression by administering a gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy has been studied to reduce the gonadotoxic impact of chemotherapy thus diminishing the chance of developing POI. Despite more than 30 years of research in both preclinical and clinical settings, the performance of this strategy has remained highly debated until recently. In particular, the potential mechanisms of action for the protective effects of GnRHa during chemotherapy are still not clearly identified. Nevertheless, important novel research efforts in the field have better elucidated the role of this option that is now endorsed for clinical use by several guidelines.

This manuscript aims at providing an extensive overview of the literature on the use of temporary ovarian suppression with GnRHa during chemotherapy in cancer patients by addressing its biological rationale, the available preclinical and clinical evidence as well as the still existing grey zones in this field that future research efforts should address.

Introduction

As a consequence of the improved survival outcomes, a significant proportion of cancer survivors face the long-term side-effect of anticancer treatments making survivorship issues an area of crucial importance to be addressed by all health care providers dealing with these patients. In women diagnosed during their reproductive years, a possible additional side effect associated with the use of anticancer therapies is the occurrence of chemotherapy-induced premature ovarian insufficiency (POI) [1]. Importantly, besides infertility, POI development has several other negative consequences on the quality of life and wellbeing of young patients being associated with menopausal symptoms as well as risk of osteoporosis, cognitive dysfunction and cardiovascular disease [2]. According to major international guidelines, POI risk should be discussed as early as possible after diagnosis with all young patients for then offering the available strategies to reduce the burden of this side effect to those who are interested [3,4].

Embryo and oocyte cryopreservation are available strategies for fertility preservation in cancer patients but they cannot prevent the risk of chemotherapy-induced POI with its associated psychosocial and menopause-related concerns beyond infertility. Temporary ovarian suppression obtained by administering a gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy has been studied as a strategy to reduce the gonadotoxic impact of chemotherapy thus diminishing the chance of developing POI. Despite a long debate on this topic, important novel research efforts in the field have better clarified

* Corresponding author at: Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Boulevard de Waterloo 121, 1000 Brussels, Belgium.
E-mail address: matteo.lambertini85@gmail.com (M. Lambertini).
[1] Co-first authors.

https://doi.org/10.1016/j.ctrv.2018.11.006
Received 12 July 2018; Received in revised form 7 November 2018; Accepted 30 November 2018

the role of temporary ovarian suppression with GnRHa during chemotherapy that is now endorsed for clinical use by several guidelines [4–6].

This manuscript aims at providing an extensive overview of the literature on the use of temporary ovarian suppression with GnRHa during chemotherapy in cancer patients by addressing its biological rationale, the available preclinical and clinical evidence as well as the still existing grey zones in this field that future research efforts should address.

Biological rationale

In human adult ovaries, the large majority of the follicles are quiescent, at the primordial stage. The activation of these follicles is precisely controlled to maintain an equilibrium between growing and quiescent follicles during the reproductive life. After reaching preantral stage, follicle development is dependent on gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) that stimulate the proliferation of granulosa cells, the differentiation of theca cells and steroidogenesis. The mechanisms of chemotherapy-induced POI involve all follicular stages and cell types, impairing both ovarian reserve and hormonal function through direct and indirect damages [7]. Proliferating granulosa cells and also theca cells of growing follicles are particularly sensitive to chemotherapy such as alkylating or platinum agents [8,9]. Therefore, pharmacological protection is challenging as it should reduce gonadotoxicity at various levels.

Up to date, the mechanism of action for the protective gonadal effect of temporary ovarian suppression with GnRHa during chemotherapy remains not fully clarified. According to the two main hypotheses, this strategy may have both indirect and direct effects on the ovaries (Fig. 1).

Indirect effect

The protective gonadal effect of GnRHa use during chemotherapy was first proposed based on the assumption that prepubertal status might prevent the ovarian damage induced by cytotoxic agents. Specifically, by suppressing the activity of the hypothalamic-pituitary-gonadal (HPG) axis, GnRHa can simulate a prepubertal hormonal environment in which the follicles would be maintained at the quiescent stage and thus would be less vulnerable to chemotherapy-induced gonadotoxicity [10]. However, this theory is widely debated since the recruitment of primordial follicles is gonadotropin-independent and occurs irrespectively of FSH levels [11]. In the absence of FSH, follicles and oocytes can grow up to the early antral stage in mice as FSH is only required for late follicular development [12]. Therefore, this

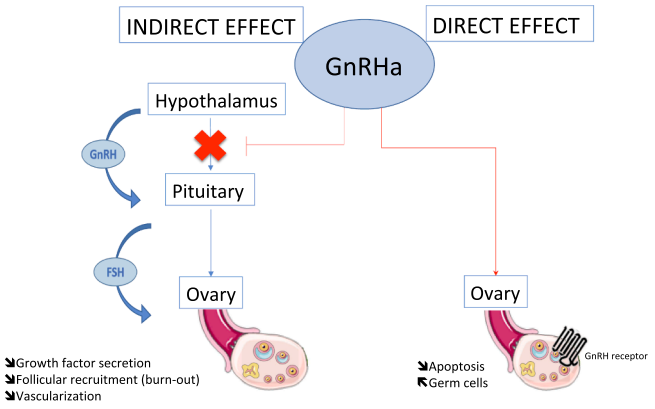

Fig. 1. Hypothesized indirect and direct mechanisms of action for the protective gonadal effect of temporary ovarian suppression with GnRHa during chemotherapy. Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist.

experimental evidence did not support the hypothesis that GnRHa act by maintaining the quiescence of primordial follicles through the inhibition of HPG axis. Nevertheless, FSH suppression obtained by administering GnRHa might prevent chemotherapy-induced damage on the early growing follicles by slowing down the proliferation rate of follicular cells and, therefore, indirectly preventing an accelerated recruitment of the quiescent follicular pool [12]. Specifically, chemotherapy-induced apoptosis of the granulosa cells surrounding the oocytes in the growing follicles is associated with a drop in estrogen secretion [13]. In the absence of GnRHa co-treatment, the decrease in estrogen levels leads to the increase of FSH secretion trough the removal of the negative feedback on the pituitary gland. The subsequent increase of FSH levels can then stimulate the proliferation of granulosa cells in the growing follicles thus further increasing their sensitivity to chemotherapy. Therefore, GnRHa co-treatment might reduce the damage on growing follicles by maintaining FSH at a low level [13]. Although experimental evidence is still lacking to confirm this hypothesis, more recent animal studies have shown a protective effect of gonadotropins against chemotherapy-induced apoptosis also in quiescent follicles [14].

Besides estrogens, growing follicles secrete also other important factors including the anti-mullerian hormone (AMH) that can negatively regulate the recruitment of primordial follicles [15]. In humans, dynamic changes in AMH levels occur during the first 4 weeks of GnRHa treatment with an initial decrease followed by an increase of about 30% after 4 weeks; on the contrary, gonadotropin levels decline of approximately 40–50% after 2 weeks of GnRHa treatment [16]. In women treated for endometriosis, similar AMH levels maintained within normal ranges were shown after 4 and 8 weeks of GnRHa treatment suggesting that the regulation of the growing follicles pool was poorly affected by long-term GnRHa administration [17]. However, a dramatic reduction in AMH levels is rapidly observed after chemotherapy due to the damage on growing follicles that leads to the massive recruitment of primordial follicles into the growing pool (a phenomenon known as “burnout effect” of chemotherapy [18]). Therefore, by preventing chemotherapy-induced damage of the early growing follicles that secrete AMH, GnRHa might reduce the recruitment of primordial follicles thus limiting the burnout effect. However, this hypothesis has also been challenged by experimental and clinical observations showing a drop of AMH levels during chemotherapy irrespectively of GnRHa administration. Nevertheless, studies in rats showed that GnRHa treatment was associated with a diminished decreased in AMH levels induced by cyclophosphamide, thus supporting a potential protective effect of GnRHa through the regulation of AMH levels during chemotherapy [19].

Another potential indirect mechanism for the protective gonadal effect of this strategy is represented by a decrease in utero-ovarian perfusion induced by GnRHa treatment with subsequent possible reduced exposure of the follicles to the gonadotoxic effect of chemotherapy [13]. Experiments in rats showed that GnRHa inhibited estrogen-induced increase of ovarian perfusion and endothelial vessel area [20]. In humans, some studies reported a significant reduction in ovarian artery blood flow after short- and long-term administration of GnRHa [21,22], but others did not confirm these findings [23,24]. Although reducing the exposure to chemotherapy could have a protective effect on follicular pool, decreasing ovarian perfusion may also have a detrimental effect on chemotherapy-induced ovarian fibrosis. Notably, one of the mechanisms responsible for chemotherapy-induced ovarian injury is represented by blood-vessel damage in the ovaries [25]. GnRHa administration can decrease mRNA expression of the vascular endothelial growth factor (VEGF) as shown in both *in vivo* rat experiments [19] and *in vitro* culture models of human granulosa cells [26]. Therefore, the increased VEGF expression observed in response to doxorubicin-induced vascular ovarian damage in order to promote neovascularization can be altered by GnRHa use with potential increased ovarian injury [19]. Nevertheless, the limited available data

and the small sample size of these studies do not allow drawing definitive conclusions on this regard.

Direct effect

The protective effect of temporary ovarian suppression with GnRHa during chemotherapy may also be exerted directly through the GnRH receptors (GnRHR) that are present in the ovaries. The presence of GnRHR in the granulosa cells of ovarian follicles at different stages and in the interstitial cells has been described in several species including rodents and humans [27]. Although the direct effect in the ovaries remains poorly understood, GnRHa administration appears to influence folliculogenesis and apoptosis. Altogether, data from several studies in rats suggested that GnRH can have an inhibitory action on immature follicles by decreasing steroidogenesis and GnRHR expression as well as a stimulatory action on mature follicles by promoting oocyte maturation and follicular rupture [28]. In addition, the presence of GnRHR on tumor cells derived from the endometrium and the ovaries as well as the evidence of an anti-tumor effect of GnRH and its analogues suggest a possible direct anti-apoptotic role [29]. Specifically, GnRHa administration might directly protect the ovaries from chemotherapy-induced gonadotoxicity by decreasing apoptotic events and mitochondrial stress. It has been speculated that GnRHa could upregulate anti-apoptotic molecules such as sphingosine-1-phosphate (S1P) [30]. S1P is an inhibitor of the ceramide pathway implicated in chemotherapy-induced apoptosis in the ovaries; moreover, this molecule is known for its angiogenic action and has shown to protect primordial follicles after xenotransplantation of human ovarian tissue by improving neoangiogenesis [31]. Exposure of follicles to S1P prevents cyclophosphamide- and doxorubicin-induced oocyte death *in vivo* in different species [32]. In addition, oocytes without expression of sphingomyelinase (required for ceramide generation) are resistant to doxorubicin-induced apoptosis *in vitro* [33]. Nevertheless, despite the intriguing hypothesis, there is no experimental evidence available yet that GnRHa-induced activation of GnRHR in the ovaries is associated with an increased expression of S1P or other anti-apoptotic factors.

Another potential suggested direct mechanism for the gonadal protection of GnRHa co-treatment is related to the possible effect on ovarian primordial germ cells. Although the conventional concept of ovarian reserve argues for a finite and non-renewable pre- or peri-natal stock of primordial follicles that varies according to species, this statement has been challenged by reports showing the presence of primordial germ cells in adult ovaries [34]. It has been speculated that GnRHa might regulate these germ cells by interacting with crucial pathways (e.g. the PI3K/Akt/mTOR pathway) implicated in cell growth/survival and primordial follicle activation after chemotherapy exposure [35–37]. However, while interaction between pathways involved in follicular activation and GnRHR has been described in various cell types, none has been biologically proven in the ovaries.

Preclinical evidence

In the 80s–90s, several experiments in rats and monkeys provided evidence on the efficacy of GnRHa use in protecting the ovaries from chemotherapy-induced damage [38–42] opening the door to its subsequent clinical development. However, subsequent preclinical experiments reported conflicting results so that after more than 30 years of research in the field, the mechanism of action of this strategy remains controversial.

Experimental preclinical data in female mice and rats

Rodents represent the most studied model in reproductive biology. Several *in vivo* experimental studies have been conducted in both female mice (Table 1) [9,19,43–52] and rats (Table 2) [38,39,41,53–62] treated with chemotherapy.

In mice, the majority of the studies showed a positive effect for GnRHa treatment in preventing busulfan-, cisplatin-, docetaxel-, and cyclophosphamide-induced depletion of primordial follicles [44–49,51] with a study suggesting that the beneficial protective gonadal effect may depend on the dose of administered chemotherapy [43]. A recent study in mice showed that co-administration of GnRHa during chemotherapy improved oocyte quality and early embryo development after exposure to cyclophosphamide [46]. After ovarian hyperstimulation, both fertilization and cleaved embryo rates were increased in mice previously treated with GnRHa and cyclophosphamide compared to those exposed to cyclophosphamide alone [46]. In addition, concomitant administration of GnRHa showed not to interfere with the

Table 1
Preclinical studies in female mice evaluating temporary ovarian suppression with GnRHa during chemotherapy.

Authors	Type of gonadotoxic treatment	Main results	Overall results
Yuce et al., 2004	Cyclophosphamide	* Small protection of primordial follicles	Protection (only against high dose of cyclophosphamide)
Danforth et al., 2005; Kishk et al., 2013; Hasky et al., 2015; Kanter et al., 2016	Cyclophosphamide	* Dose-dependant protection of the ovarian reserve * Slight protection of growing follicles * Preservation of AMH levels * Preservation of fertilization rate, early embryo development and improvement of oocyte quality	Protection
Tan et al., 2010	Busulfan	* Protection of primordial and primary follicles	Protection
Lin et al., 2012; Zhang et al., 2013	Cisplatin	* Protection of quiescent and growing follicles * Preservation of AMH levels * No difference in proliferation and apoptosis in the ovaries	Protection
Detti et al., 2014; Horicks et al., 2015; Horicks et al., 2018	Cyclophosphamide	* No protection of quiescent and growing follicles * No protection of FSH and AMH levels * FSH deficiency does not protect ovarian reserve * *In vitro* exposure to GnRHa does not preserve follicular survival * No difference in proliferation and apoptosis in the ovaries	No protection
Hasky et al., 2015	Doxorubicin	* Compromise vascular recovery * No preservation of AMH levels	No protection
Park et al., 2017	Docetaxel	* Protection of total follicles * Preservation of proliferation within follicles * Decrease of double-strand DNA breaks	Protection

Abbreviations: AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist.

Table 2
Preclinical studies in female rats evaluating temporary ovarian suppression with GnRHa during chemotherapy.

Authors	Type of gonadotoxic treatment	Main results	Overall results
Ataya et al., 1985; Ataya et al., 1988; Bokser et al., 1990; Ataya et al., 1993; Knudtson et al., 2017	Cyclophosphamide	* Protection of quiescent and growing follicles * Preservation of LH and E2 levels * Preservation of pregnancy, implantation and live birth rates	Protection
Montz et al., 1991	Cyclophosphamide	* Improvement of fertility only with agonist twice a day	Partial protection
Letterie et al., 2004; Li et al., 2015; Parlakgumus et al., 2015	Cyclophosphamide	* No protection of ovarian reserve and growing follicles * No preservation of fertility * Increase in liver, pulmonary and splenic hemorrhage * No preservation of AMH levels	No protection
Matsuo et al., 2007; Li et al., 2013	Cisplatin	* Protection of ovarian reserve * Preservation of cyclicity	Protection
Ozcelik et al., 2010	Paclitaxel and/or cisplatin	* Protection of ovarian reserve (paclitaxel) * No protection of ovarian reserve (cisplatin)	Protection only against paclitaxel
Wang et al., 2014	5-fluorouracil	* Protection of ovarian reserve * Preservation of AMH and FSH levels * Decrease of apoptotic factors	Protection

Abbreviations: LH, luteinizing hormone; E2, estradiol; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone.

efficacy of chemotherapy; specifically, mice grafted with human ovarian cancer cells and treated with cisplatin alone or in combination with a GnRHa displayed a similar reduction in cancer mass [48]. However, other studies did not confirm these findings showing lack of protective effect for GnRHa against the gonadal damage induced by cyclophosphamide [9,50,52] or doxorubicin [19]. One of the most recent studies has shown that the absence of FSH did not prevent cyclophosphamide-induced ovarian damage in a FSH-deficient mouse model suggesting that the inhibition of gonadotropin secretion may not be the explanation for the ovarian protection of GnRHa treatment [52].

In rats, the first studies demonstrated no acute toxicity of cyclophosphamide on primordial follicles but rather a depletion of growing follicles; in this scenario, co-administration of GnRHa showed to preserve small follicles suggesting an inhibitory effect on the mitotic activity of granulosa cells and, as a consequence, an indirect reduction of quiescent follicle recruitment [38,39,41]. A protective effect in preserving the pool of primordial and preantral follicles was also observed after exposure to cisplatin [58] or 5-fluorouracil [61]. In addition, higher AMH levels were also observed in rats exposed to GnRHa and 5-fluorouracil as compared to those treated with 5-fluorouracil alone [61]. To enhance the protective effect of GnRHa treatment, a concomitant administration of GnRH antagonist was also proposed to avoid the initial flare-up effect of GnRHa during treatment with cisplatin [59]. The protective potential of GnRHa use on fertility has also been investigated; chemotherapy disrupted estrous cycles and reduced fertility and litter size but these effects were prevented by pretreatment with GnRHa [53,54] or by a combination of GnRHa and GnRH antagonist [59]. However, these results were not confirmed by others studies [55,57]. On the other hand, one study has even suggested an increased follicular depletion after a transitory protective effect of GnRHa in rats exposed to cyclophosphamide with also no fertility improvement [56].

Experimental preclinical data in female primates and human models

More limited experimental preclinical data are available in female primates and human models (Table 3) [42,63,64].

In rhesus monkeys, the concurrent use of GnRHa and cyclophosphamide showed to significantly reduce chemotherapy-induced loss of primordial follicles from 65% to 29% [42]. In human granulosa cells exposed *in vitro* to GnRHa prior to doxorubicin, estradiol levels after FSH stimulation were preserved as compared to those exposed to chemotherapy alone [63]. However, more recently, no direct protective effect of GnRHa use was observed in human cortical fragments and granulosa cell lines exposed *in vitro* to different gonadotoxic treatments [64]. In this study, chemotherapy caused follicular depletion, impaired hormonal levels, upregulated apoptotic factors and decreased vascular density of human ovarian tissue; however, none of these parameters was improved by concurrent GnRHa administration [64].

Table 3
Preclinical studies in female primates and human models evaluating GnRHa effect during chemotherapy.

Authors	Model	Type of gonadotoxic treatment	Main results	Overall results
Ataya et al., 1995	*In vivo* study in rhesus monkeys	Cyclophosphamide	* Protection of ovarian reserve * Preservation of FSH, E2 and P levels * Interruption of cyclicity	Protection
Imai et al., 2007	*In vitro* study on human granulosa cells	Doxorubicin	* Direct preservation of E2 levels after FSH stimulation	Protection
Bildik et al., 2015	*In vitro* study on human granulosa cells and ovarian tissue fragments	Cyclophosphamide Paclitaxel 5-fluorouracil TAC regimen	* No protection of ovarian reserve * No preservation of AMH, E2 and P levels * No upregulation of anti-apoptotic genes * No preservation of the vascular density	No protection

Abbreviations: FSH, follicle-stimulating hormone; E2, estradiol; P, progesterone; AMH, anti-Mullerian hormone; GnRHa, gonadotropin-releasing hormone agonist; TAC, docetaxel, doxorubicin, cyclophosphamide.

Critical appraisal of the available preclinical evidence

Taken together, most of the available preclinical evidence supports the ovarian protective effect of administering GnRHa concurrently with different chemotherapy agents. However, due to differences in terms of experimental models, type and dose of chemotherapy used as well as way and duration of GnRHa administration, significant discrepancies have been observed between the various studies.

Mice and rats have been the most used models, with a greater predominance of the former in more recent studies and of the latter in the early experiments. Rodents, mainly mice and in a lesser extent rats, have proved to be valuable models for research in the reproductive field with the main advantages of a large amount of available material, the ease of breeding, and the possibility of genetic manipulation to study the role of specific genes. Although both are rodents, differences between these two species and compared to the humans exist [65] and may explain some discrepant results. Rodents are polyovulatory species with a shorter estrous cycle and folliculogenesis as well as with less fibrous and dense ovaries as compared to humans. These characteristics might impact the experimental findings due to differences in follicular regionalization, in the relative timing of exposure in comparison to the duration of folliculogenesis and in the penetration of the drugs when using *in vitro* models.

Few experimental studies have documented the inhibitory effect of GnRHa administration on the HPG axis. While gonadotropin suppression is well documented in humans during GnRHa treatment [66], data in rodents are sparse. Some authors did not observe any change in FSH and estradiol levels when these animals were treated with GnRHa [9,41,58], while others showed a decrease in pituitary GnRHR and estradiol levels [67]. A recent study showed a decrease of FSHb and LHb mRNA expression in the pituitary of mice treated with GnRHa but the impact on circulating hormone levels and on follicular growth was not reported [19]. The presence of antral follicles was previously described in animal models during GnRHa treatment [9,60,68] suggesting that HPG axis is not completely inhibited.

Parameters used to evaluate chemotherapy-induced ovarian damage in humans are not only menstrual cycle recovery and FSH but also AMH levels. AMH reflects the number of ovarian growing follicles and is a reliable indicator of ovarian reserve as it is stable during the ovarian cycle. In experimental animal studies, AMH level is rarely measured and ovarian reserve is evaluated based on follicular count at only one specific time-point. Moreover, only a few experimental animal studies have reported on the long-term effects of GnRHa co-treatment. Hasky and colleagues studied the gonadoprotective effects of GnRHa against doxorubicin- and cyclophosphamide-induced damage in prepubertal mice [19]. Long-term monitoring of AMH levels suggested ovarian reserve depletion through both direct insult and accelerated follicular activation. When mice were pre-treated with GnRHa, AMH level was maintained in the long run (up to 9 months of follow-up), but this protective effect was not observed in mice exposed to doxorubicin [19]. These interesting results may also suggest potential differences in the protective effect of GnRHa according to the type of chemotherapy agents. Depending on the mechanisms of follicular depletion involved, these findings further highlight the challenge of using accurate ovarian markers according to species and experimental design.

The direct action of GnRHa in the ovaries through GnRHR has been poorly investigated using *in vitro* follicle models and these experiments were inconclusive [52,64]. Although GnRHRs were identified in growing follicles but not in primordial follicles, they were also observed in perinatal ovaries [52] and ovarian epithelium [69] supporting the hypothesis of a potential direct protective effect of GnRHa administration during chemotherapy. However, the role of these ovarian receptors as well as the pathways involved after their activation remain unclear. In granulosa cells, despite the presence of similar GnRHRs as in the pituitary gland, their intracellular signaling pathway appears to be different [70]. In addition, the structural differences in GnRHRs between human and rodents may also explain the difference in their level of expression. The presence of an extra lysine at position 191 in human GnRHRs appears to be responsible for a lower expression of the receptor as well as for a faster internalization [71]. In the human ovary, GnRHRs are localized in granulosa cells from the antral stage and in the corpus luteum [72] but expression in rats is broader and has been found in all follicular types except in the primordial follicles [28]. In regard to the activated pathway, stimulation of mouse granulosa cells with GnRHa did not induce a detectable rise in cAMP levels [52,73]. However, a recent study in humans reported increased intracellular cAMP levels in cortical pieces and in granulosa cell lines following GnRHa stimulation [64] thus suggesting again potential different actions of the GnRH/GnRHR system in rodents and humans. Therefore, the role and the signaling pathway of GnRHRs in the ovaries need to be further investigated in both animals and human models.

Clinical evidence

In premenopausal women, several clinical research efforts have been conducted in this setting, not only in cancer patients but also in women receiving chemotherapy for autoimmune diseases. For premenopausal cancer patients, the majority of the studies have been conducted in young women with breast cancer but important evidence exists also for those with hematological malignancies; conversely, limited data are available for cancer patients diagnosed with other solid tumors.

Randomized trials

Breast cancer

A total of 14 different randomized trials have been conducted to investigate the clinical efficacy of temporary ovarian suppression with GnRHa during chemotherapy as a strategy to preserve ovarian function and potential fertility in premenopausal breast cancer patients (Table 4) [74–89].

In the majority of the trials, chemotherapy-induced POI was defined based only on menstrual function after treatment with few studies that used a composite endpoint (i.e. amenorrhea and post-menopausal hormonal levels) for its definition. The timing of POI evaluation ranged from 6 months up to more than 5 years after the end of chemotherapy. The majority of the trials had a small sample size with less than 100 randomized patients. Median age of the included patients was close to 40 years in the majority of the trials. Anthracyline- and cyclophosphamide-based chemotherapy was the most commonly used regimen. The administered GnRHa was goserelin in 8 trials, triptorelin in 5 and leuprolide acetate in one.

Globally, all but 4 trials showed that temporary ovarian suppression with GnRHa during chemotherapy was effective in reducing the risk of chemotherapy-induced POI. Nevertheless, limited evidence exists on the fertility preservation potential of this strategy. Notably, post-treatment pregnancies was a pre-planned secondary endpoint in only one study, the POEMS/SWOG S0230 trial [86,87]. Moreover, it should be highlighted that the majority of the studies included a limited number of patients and reported results of their primary endpoint (i.e. chemotherapy-induced POI) after a short follow-up so that the fertility preservation potential of this strategy could not be assessed.

In the past, two major safety concerns were raised for administering GnRHa during chemotherapy in breast cancer patients with estrogen receptor-positive disease: a potential antagonism with concurrent use of systemic cytotoxic therapy and endocrine agents as well as the possible detrimental prognostic effect of preventing chemotherapy-induced POI development [90]. These are also the reasons for allowing the inclusion of only patients with estrogen receptor-negative breast cancer in some of the randomized trials. The TEXT and SOFT trials have recently

Table 4
Randomized trials evaluating temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients.

Authors	Type of disease	POI definition (timing of its evaluation)	Timing POI evaluation (months)	Treatment regimen	No. patients	Median age (years)	Main results (GnRHa vs. control)	Overall results
Li M et al. 2008	Breast cancer	Amenorrhea	12	CT + goserelin CT	31 32	40 39	• POI rate: 32.1% vs. 53.1% (p = 0.027)	Protection
Badawy A et al. 2009	Breast cancer	Amenorrhea and no resumption of ovulation	8	CT + goserelin CT	39 39	30 29.2	• POI rate: 11.4% vs. 66.6% (p < 0.001)	Protection
Sverrisdottir A et al. 2009	Breast cancer	Amenorrhea	Up to 36	CT + goserelin (± tamoxifen) CT (± tamoxifen)	51 43	45 45–46	• POI rate: 64% (93%) vs. 90% (87%) (p = 0.006)	Protection
Gerber B et al. 2011	Breast cancer	Amenorrhea	6	CT + goserelin CT	30 30	35 38.5	• POI rate: 30% vs. 43.3% (p = 0.142); OR (control vs. GnRHa) 1.24, 95% CI 0.39–3.90 • Pregnancies: 1 vs. 1	No protection
Sun JB et al. 2011	Breast cancer	Amenorrhea	12	CT + goserelin CT	11 10	38 37	• POI rate: 27.3% vs. 50.0% (p = 0.039)	Protection
Del Mastro L et al. 2011 Lambertini M et al. 2015	Breast cancer	Amenorrhea and postmenopausal levels of FSH and E2	12	CT + triptorelin CT	148 133	39 39	• POI rate: 8.9% vs. 25.9% (p < 0.001); OR 0.28, 95% CI 0.14–0.59 • Pregnancies: 8 vs. 3 (p = 0.20); HR 2.40, 95% CI 0.62–9.22 • DFS events: 36 vs. 29 (5-y DFS 80.5% vs. 83.7%) (p = 0.72); HR 1.10, 95% CI 0.67–1.79	Protection
Munster P et al. 2012	Breast cancer	Amenorrhea	24	CT + triptorelin CT	27 22	39 38	• POI rate: 15% vs. 14% (p = 0.32) • Pregnancies: 0 vs. 2	No protection
Elgindy EA et al. 2013	Breast cancer	Amenorrhea	12	CT + triptorelin (± GnRHa antagonist) CT	50 50	33 32	• POI rate: 20%/16% vs. 20%/20% (p = 1.00/p = 0.71); RR 1.00, 95% CI 0.76–1.32/RR 0.95, 95% CI 0.73–1.24 • Pregnancies: 2 vs. 1	No protection
Song G et al. 2013	Breast cancer	Amenorrhea and postmenopausal levels of FSH and E2	12	CT + leuprolide acetate CT	89 94	40.3 42.1	• POI rate: 16.9% vs. 28.7% (p < 0.01)	Protection
Jiang FY et al. 2013	Breast cancer	Amenorrhea	–	CT + triptorelin CT	10 11	– –	• POI rate: 10.0% vs. 45.5% (p = 0.05)	Protection
Karimi-Zarchi M et al. 2014	Breast cancer	Amenorrhea	6	CT + triptorelin CT	21 21	37	• POI rate: 9.5% vs. 66.7% (p < 0.001)	Protection
Moore HCF et al. 2015 Moore HCF et al. 2018	Breast cancer	Amenorrhea and postmenopausal levels of FSH	24	CT + goserelin CT	105 113	37.6 38.7	• POI rate: 8% vs. 22% (p = 0.04); OR 0.30, 95% CI 0.09–0.97 • Pregnancies: 23 vs. 13 (p = 0.04); OR 2.34, 95% CI 1.07–5.11 • DFS events: 12 vs. 23 (5-y DFS 88.1% vs. 78.6%) (p = 0.09); HR 0.55, 95% CI 0.27–1.10 • OS events: 8 vs. 18 (5-y OS 91.7% vs. 83.1%) (p = 0.06); HR 0.45, 95% CI 0.19–1.04	Protection
Leonard RCF et al. 2017	Breast cancer	Amenorrhea and postmenopausal levels of FSH	Between 12 and 24	CT + goserelin CT	103 118	37.9 38.8	• POI rate: 18.5% vs. 34.8% (p = 0.048) • Pregnancies: 7 vs. 5 • OS events: 9 vs. 15	Protection
Zhang Y et al. 2018	Breast cancer	Amenorrhea and postmenopausal levels of FSH and E2	36–72	CT + goserelin CT	108 108	37.5 39	• POI rate: 23.1% vs. 22.8% (p = 0.969); OR 1.13, 95% CI 0.54–2.37 • DFS events: 23 vs. 17 (5-y DFS 78.2% vs. 84.5%) (p = 0.201); HR 1.52, 95% CI 0.80–2.86 • OS events: 7 vs. 5 (5-y OS 96.0% vs. 95.3%) (p = 0.411); HR 1.62, 95% CI 0.51–5.16	No protection

Abbreviations: POI, premature ovarian insufficiency; GnRHa, gonadotropin-releasing hormone agonist; CT, chemotherapy; FSH, follicle-stimulating hormone; E2, estradiol; DFS, disease-free survival; OS, overall survival; OR, odds ratio; CI, confidence intervals; HR, hazard ratio; RR, risk ratio.

dispelled these concerns showing no difference in the survival outcomes of premenopausal women with estrogen receptor-positive breast cancer who received GnRHa concurrently or sequentially to chemotherapy [91]. Similarly, no survival difference was observed in the two trials that assessed these endpoints in estrogen receptor-positive breast cancer patients treated with chemotherapy alone or with concurrent GnRHa [80,89]. Nevertheless, the majority of the patients included in these analyses were also treated with GnRHa as part of adjuvant endocrine therapy in the case of ovarian function resumption after chemotherapy [80,89]. Therefore, subsequent ovarian function suppression as part of adjuvant endocrine therapy should be considered for patients with estrogen receptor-positive breast cancer who received temporary ovarian suppression with GnRHa during chemotherapy.

Notably, so far, there is the lack of data on the efficacy of using temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients with hereditary cancer syndromes such as those carrying deleterious germline *BRCA* mutations [92,93]. Some evidence suggests that baseline ovarian reserve of *BRCA*-mutated breast cancer patients can be partly reduced with subsequent potential higher risk of chemotherapy-induced POI [94]. The protective gonadal effect of temporary ovarian suppression with GnRHa during chemotherapy in *BRCA*-mutated patients or women with other hereditary cancer syndromes should be investigated in the coming future within the currently available randomized trials.

Lymphoma and other malignancies

More limited evidence exists on the role of temporary ovarian suppression with GnRHa during chemotherapy as a strategy to preserve ovarian function and potential fertility in women with tumors other than breast cancer (Table 5) [95–100]. The majority of the data are available for lymphoma patients with only one trial conducted in women with ovarian cancer.

A total of 4 different randomized trials were conducted in young women with hematological malignancies [95–99]. In 3 of these trials, only premenopausal women with Hodgkin lymphoma were included; conversely, in the study by Demeestere and colleagues [98,99], both patients with Hodgkin and non-Hodgkin lymphoma were randomized. Chemotherapy-induced POI was defined based on menstrual function after treatment in two trials and on post-menopausal hormonal levels in the other two studies (i.e. none of them used a composite endpoint with amenorrhea and post-menopausal hormonal levels). Similarly to the breast cancer trials, the timing of POI evaluation was highly variable, ranging from 6 months up to more than 5 years after the end of chemotherapy. All the trials included a small number of patients exceeding 30 participants only in the study by Demeestere and colleagues [98,99]. Median age at study entry was approximately 25 years. Patients received regimens with different gonadotoxicity, from low (e.g. ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine) to high (e.g. conditioning regimens for hematopoietic stem cell transplantation) risk regimens. The administered GnRHa was triptorelin in 2 trials, goserelin and buserelin in the others.

None of these trials reported a protective effect for temporary ovarian suppression with GnRHa during chemotherapy with limited data on post-treatment pregnancies [99].

In premenopausal women with other solid tumors, only one small randomized trial investigated the clinical efficacy of temporary ovarian suppression with GnRHa during chemotherapy in patients with ovarian cancer [100]. A total of 30 patients with different histology of ovarian tumors and a median age of 21–22 years were randomized to receive chemotherapy with or without the GnRHa triptorelin. Both cyclophosphamide- and platinum-based chemotherapy regimens were allowed. Six months after chemotherapy, all the patients in the GnRHa arm had normal menstrual bleeding, while 33% of women treated with chemotherapy only had permanent treatment-induced POI. No data on post-treatment pregnancies were reported.

Table 5
Randomized trials evaluating temporary ovarian suppression with GnRHa during chemotherapy in cancer patients with diseases other than breast cancer.

Authors	Type of disease	POI definition (timing of its evaluation)	Timing POI evaluation (months)	Treatment regimen	No. patients	Median age (years)	Main results (GnRHa vs. control)	Overall results
Waxaman JH et al. 1987	HL	Amenorrhea	Up to 36	CT + buserelin	8	28.5	• POI rate: 50% vs. 33.3%	No protection
				CT	10	25.9	• Pregnancies: 0 vs. 1	
Loverro G et al. 2007*	HL	Amenorrhea	NR	CT + triptorelin	14	24.3	• POI rate: 0% vs. 46%	No protection
				CT	15	24.3	• Pregnancies: 0 vs. 2	
Behringer K et al. 2010	HL	AMH levels below normal range	12	CT + goserelin	11	25.3	• POI rate (AMH): 100% vs. 100%	No protection
				CT + OC	12	26.0	• Amenorrhea rate: 30.0% vs. 33.3%	
							• Pregnancies: 0 vs. 0	
Demeestere I et al. 2013 Demeestere I et al. 2016	HL and NHL	Postmenopausal levels of FSH	12	CT + triptorelin + OC	45	25.6	• 1-y POI rate: 20% vs. 19% (p = 1.00)	No protection
				CT + OC	39	27.3	• 1-y AMH at ≥ 1 ng/mL: 50.0% vs. 13.3% (p = 0.023)	
							• Long-term POI rate: 19.4% vs. 25.0% (p = 0.763); OR (control vs. GnRHa) 0.70, 95% CI 0.15–3.24	
							• Pregnancies: 17 vs. 15 (p = 0.467)	
							• OS events: 4 vs. 2	
Gilani M et al. 2007	Ovarian cancer	Amenorrhea and postmenopausal levels of FSH	6	CT + triptorelin	15	21	• POI rate: 0% vs. 33% (p = 0.02)	Protection
				CT	15	22		

Abbreviations: POI, premature ovarian insufficiency; GnRHa, gonadotropin-releasing hormone agonist; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; CT, chemotherapy; OC, oral contraceptives; OS, overall survival; OR, odds ratio; CI, confidence intervals.

* The inconsistencies in methods and results pose strong doubts about the randomized nature of the study.

Table 6
Meta-analyses evaluating temporary ovarian suppression with GnRHa during chemotherapy in cancer patients.

Authors	Type of disease	No. included studies (No. RCTs)	No. patients	Main results (GnRHa vs. control)	Overall results
Clowse MEB et al. 2009	Autoimmune disease, HL and NHL	9 (2)	366	• POI rate: 7% vs. 52%; RR 1.68, 95% CI 1.34–2.10 • Pregnancies: 36 (22%) vs. 22 (14%); RR 1.65, 95% CI 1.03–2.60	Protection
Ben-Aharon I et al. 2010	Autoimmune disease, breast cancer, HL and NHL	16 (5)	681	• POI: RR 0.26, 95% CI 0.14–0.49 • POI (RCTs only): RR 0.55, 95% CI 0.22–1.38 • Pregnancies: 47 (22%) vs. 25 (12%); RR 1.51, 95% CI 1.01–2.28 • Pregnancies (RCTs only): 2 (4%) vs. 9 (18%); RR 0.33, 95% CI 0.10–1.08	Protection (not in RCTs)
Kim SS et al. 2010	Autoimmune disease, breast cancer, HL and NHL	11 (3)	654	• POI rate: 10% vs. 53%; OR 10.57, 95% CI 5.22–21.39 • POI (RCTs only): 13% vs. 57%; OR 5.76, 95% CI 0.47–71.03	Protection
Bedaiwy et al. 2011	Breast cancer, ovarian cancer, and HL	6 (6)	340	• POI rate: 43% vs. 65%; OR 3.46, 95% CI 1.13–10.57 • Pregnancies: 1 (2%) vs. 4 (7%); OR 0.44, 95% CI 0.07–2.59	Protection (not for pregnancy)
Chen H et al. 2011	Breast cancer, ovarian cancer and HL	4 (4)	157	• POI rate: 6% vs. 55%; RR 1.90, 95% CI 1.33–2.70 • Pregnancies: 0 (0%) vs. 2 (13%); RR 0.21, 95% CI 0.01–4.09	Protection (not for pregnancy)
Yang B et al. 2013	Breast cancer	5 (5)	528	• POI: RR 0.40, 95% CI 0.21–0.75 • Pregnancies: RR 0.96, 95% CI 0.20–4.56	Protection (not for pregnancy)
Wang C et al. 2013	Breast cancer	7 (7)	677	• POI: OR 2.83, 95% CI 1.52–5.25	Protection
Zhang Y et al. 2013	HL and NHL	7 (3)	434	• POI rate: 14% vs. 48%; OR 0.32, 95% CI 0.13–0.77 • Pregnancies: 22 (14%) vs. 15 (11%); OR 1.13, 95% CI 0.53–2.38	Protection (not for pregnancy)
Sun X et al. 2014	Breast cancer, ovarian cancer, and HL	8 (8)	621	• POI rate: 10% vs. 27%; RR 0.45, 95% CI 0.22–0.92 • Pregnancies: 6 (2%) vs. 6 (3%); RR 0.93, 95% CI 0.33–2.61	Protection (not for pregnancy)
Del Mastro L et al. 2014	Breast cancer, ovarian cancer, HL and NHL	9 (9)	765	• POI rate: 22% vs. 37%; OR 0.43, 95% CI 0.22–0.84 • Pregnancies: 10 vs. 3	Protection
Vitek WS et al. 2014	Breast cancer (hormone receptor-negative only)	4 (4)	252	• POI rate: 24% vs. 27%; OR 1.47, 95% CI 0.60–3.62	No protection
Elgindy E et al. 2015	Breast cancer, ovarian cancer, HL and NHL	10 (10)	907	• POI rate: 32% vs. 40%; RR 1.12, 95% CI 0.99–1.27 • Pregnancies: 30 (7%) vs. 20 (5%); RR 1.63, 95% CI 0.94–2.82	No protection
Shen YW et al. 2015	Breast cancer	11 (11)	1062	• POI rate: 30% vs. 45%; OR 2.57, 95% CI 1.65–4.01 • Pregnancies: 26 (9%) vs. 16 (6%); OR 1.77, 95% CI 0.92–3.40	Protection (not for pregnancy)
Lambertini M et al. 2015	Breast cancer	12 (12)	1231	• POI rate: 19% vs. 34%; OR 0.36, 95% CI 0.23–0.57 • Pregnancies: 33 (9%) vs. 19 (6%); OR 1.83, 95% CI 1.02–3.28	Protection (also for pregnancy)
Munhoz RR et al. 2016	Breast cancer	7 (7)	856	• POI rate at 6 months: 26% vs. 43%; OR 2.41, 95% CI 1.40–4.15 • POI rate at 12–24 months: 26% vs. 37%; OR 1.85, 95% CI 1.33–2.59 • Pregnancies: OR 1.85, 95% CI 1.02–3.36	Protection (also for pregnancy)
Silva C et al. 2016	Breast cancer	7 (7)[a]	1002[a]	• POI rate: 26% vs. 39%; OR 2.03, 95% CI 1.18–3.47	Protection
Bai F et al. 2017	Breast cancer, ovarian cancer	15 (15)[a]	1540[a]	• POI rate: 23% vs. 43%; OR 1.36, 95% CI 1.19–1.56 • Pregnancies: 34 (7%) vs. 19 (4%); OR 1.90, 95% CI 1.06–3.41	Protection (also for pregnancy)
Senra JC et al. 2018	Breast cancer, HL and NHL	13 (13)	1208	• POI rate: 20% vs. 34%; RR 0.60, 95% CI 0.45–0.79 • Pregnancies: 57 (11%) vs. 42 (8%); RR 1.43, 95% CI 1.01–2.02	Protection (also for pregnancy)
Hickman LC et al. 2018	Breast cancer, ovarian cancer, HL and NHL	10 (10)	1051	• POI rate: 29% vs. 39%; OR 1.83, 95% CI 1.34–2.49	Protection
Lambertini M et al. 2018	Breast cancer	5 (5)[b]	873	• POI rate: 14% vs. 31%; OR 0.38, 95% CI 0.26–0.57 • Pregnancies: 37 (10%) vs. 20 (6%); IRR 1.83, 95% CI 1.06–3.15	Protection (also for pregnancy)

Abbreviations: RCTs, randomized controlled trials; GnRHa, gonadotropin-releasing hormone agonist; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; POI, premature ovarian insufficiency; RR, relative risk/risk ratio/rate ratio; OR, odds ratio; CI, confidence intervals; IRR, incidence rate ratio.

[a] Data from the original publication (Del Mastro et al. JAMA 2011) and the updated analysis (Lambertini M et al. JAMA 2015) of the PROMISE-GIM6 trial were considered twice instead of as from the same study.

[b] Meta-analysis based on individual patient-level data.

Meta-analyses of randomized trials

Several meta-analyses have been conducted to summarize the results from the available randomized trials performed to investigate the clinical efficacy of temporary ovarian suppression with GnRHa during chemotherapy in premenopausal cancer patients (Table 6) [101–120]. The oldest meta-analyses included also prospective non-randomized studies, some were restricted to a single tumor type (i.e. breast cancer only or hematological malignancies only) while others included the results from all the randomized trials irrespectively of patient population.

Globally, all but two meta-analyses showed a protective effect of this strategy in reducing the risk of chemotherapy-induced POI in premenopausal cancer patients. The benefit was larger and clearer in the meta-analyses including only the trials conducted in breast cancer patients but was also observed in those that allowed the inclusion of the studies performed in women with hematological malignancies and ovarian cancer.

In terms of fertility preservation potential, the protective effect of GnRHa use during chemotherapy was not observed in the oldest meta-analyses; on the contrary, the most recent meta-analyses including a larger number of randomized trials and the largest studies showed also a significantly higher pregnancy rate for premenopausal women treated with GnRHa during chemotherapy.

Critical appraisal of the available clinical evidence

More than 30 years of active clinical research efforts have been performed to elucidate the role of administering GnRHa during chemotherapy to preserve ovarian function and potential fertility in premenopausal patients undergoing cytotoxic therapy.

When considering the efficacy of this strategy in reducing the risk of chemotherapy-induced POI, two important considerations should be made.

First, while consistent data proved the efficacy of this strategy in breast cancer patients, negative results were obtained in the trials conducted in women with hematological malignancies. There are both methodological and clinical potential explanations for this discrepancy. From a methodological perspective, only 4 small trials including 154 women were conducted in lymphoma patients. Therefore, lack of power is a major concern in this setting. Conversely, 14 breast cancer trials including 1647 patients are now available, with 4 studies that randomized more than 200 women. From a clinical perspective, important differences between premenopausal patients with breast cancer and those with lymphoma should be highlighted. Patients with hematological malignancies are characterized by a young age at diagnosis (approximately 25 years) and are treated with chemotherapy regimens having a low or high gonadotoxicity [1]. As these younger patients generally have robust ovarian reserve, acute POI is usually observed after high-risk treatment while ovarian function recovery occurs in most after low- or intermediate-risk treatments irrespectively of GnRHa administration. In this population, if present, the protective effect of GnRHa might be only visible after long-term follow-up (i.e. age at menopause) and its benefit in terms of fertility preservation would be limited. Conversely, premenopausal breast cancer patients are usually older at diagnosis (approximately 40 years) and receive chemotherapy regimens characterized by an intermediate risk of gonadotoxicity [121]. In this scenario, the clear although modest benefit of using temporary ovarian suppression with GnRHa during chemotherapy in reducing the risk of chemotherapy-induced POI becomes evident. Notably, in this setting, the benefit of administering GnRHa during chemotherapy has been observed irrespectively of the type of chemotherapy regimen used (i.e. including or not cyclophosphamide and/or an anthracycline) [120]. A final important clinical difference is represented by the potential negative effect of the disease itself on patients' reproductive potential; in fact, while it has been shown that lymphoma patients may have a diminished ovarian reserve even before starting anticancer therapies [122,123], this has not been described so far in breast cancer patients.

Second, no uniform and standard definition of chemotherapy-induced POI exists to date. This is reflected by the use of various definitions (that included amenorrhea in almost all cases) and timepoints of its evaluation in the different trials. However, amenorrhea is not an optimal surrogate marker for defining the gonadotoxicity of anticancer treatments [124,125]; the use of this endpoint is of particular concern when tamoxifen is given as adjuvant endocrine therapy considering the perturbation of menstrual function induced by the use of this treatment [126,127]. In the absence of a clear-cut definition, experts recommend to empirically define chemotherapy-induced POI with a composite definition of amenorrhea for ≥ 2 years and post-menopausal hormonal profile [6,128]. Only a minority of the trials reported an evaluation of menstrual function at long-term and no studies assessed the final age at menopause for the randomized patients including those who did not develop immediate chemotherapy-induced POI. In the few trials that evaluated AMH [77,82,88,96–99], no difference in post-treatment AMH values was observed between patients who received GnRHa during chemotherapy and those who were treated with systemic cytotoxic therapy alone. Nevertheless, in all these trials, AMH could be assessed only in a small proportion of the randomized patients limiting the interpretation of these results.

When considering the efficacy of temporary ovarian suppression with GnRHa during chemotherapy as a strategy for fertility preservation, available data are more limited. However, notably, the trials were not designed nor powered to assess differences in post-treatment pregnancies, pregnancy desire was not a criteria for study inclusion and most of the trials reported results at a short follow-up time without the possibility of assessing this important outcome. Although the numbers remain low, all the most recent meta-analyses reported a significantly higher number of post-treatment pregnancies in breast cancer patients who received GnRHa during chemotherapy as compared to those treated with systemic cytotoxic therapy alone [114,115,117,118,120], with no benefit in lymphoma patients [118].

Conclusions and future perspectives

After more than 30 years of research in the field, recently updated guidelines recommend the use of temporary ovarian suppression with GnRHa during chemotherapy in premenopausal breast cancer patients through systemic cytotoxic therapy [4–6]. The best candidates for this strategy are women aiming to reduce the risk of developing chemotherapy-induced POI irrespectively of their pregnancy desire. For women interested in fertility preservation, temporary ovarian suppression with GnRHa during chemotherapy should be proposed after embryo and oocyte cryopreservation as well as in patients that for different reasons have no access to fertility units. As per study design in the majority of the trials, when temporary ovarian suppression with GnRHa during chemotherapy is offered, GnRHa should be started preferably at least one week before the initiation of systemic cytotoxic therapy and prolonged until after the administration of the last chemotherapy cycle.

Limited and controversial data are available to counsel premenopausal women with tumors other than breast cancer about the protective role of this strategy. However, although extrapolation from the breast cancer trials cannot be made, it can be considered reasonable to discuss temporary ovarian suppression with GnRHa during chemotherapy as an option to reduce POI risk with all premenopausal women who are candidates to chemotherapy considering its safety profile (including the reversibility of the induced side effects) as well as

its other potential medical benefits (such as the reduction of vaginal bleeding with prevention of menometrorrhagia and the contraceptive effect).

The need for a new clinical trial with proper design and sample size has been suggested [4], but such a study would be unethical taking into account the available evidence. Nevertheless, further research efforts are warranted to collect long-term follow-up data from the already available randomized trials that could provide more solid clinical evidence on this topic. In addition, considering that the potential mechanisms of action for the protective effects of GnRHa during chemotherapy are still not clearly identified, well-designed and adequately conducted *in vitro* and *in vivo* experiments including in species other than rodents should be further encouraged in the coming years.

Acknowledgments

Matteo Lambertini acknowledges the support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet in Brussels (Belgium).

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

Matteo Lambertini served as a consultant for Teva and received speaker honoraria from Theramex outside the submitted work. All remaining authors declare no conflicts of interest.

References

[1] Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med 2016;14:1. https://doi.org/10.1186/s12916-015-0545-7.
[2] Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst 2012;104:386–405. https://doi.org/10.1093/jnci/djr541.
[3] Peccatori FA, Azim Jr HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi160–70. https://doi.org/10.1093/annonc/mdt199.
[4] Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2018;36(19):1994–2001. https://doi.org/10.1200/JCO.2018.78.1914.
[5] Lambertini M, Cinquini M, Moschetti I, Peccatori FA, Anserini P, Valenzano Menada M, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. Eur J Cancer 2017;71:25–33. https://doi.org/10.1016/j.ejca.2016.10.034.
[6] Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso M-J, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast 2017;35:203–17. https://doi.org/10.1016/j.breast.2017.07.017.
[7] Ben-Aharon I, Shalgi R. What lies behind chemotherapy-induced ovarian toxicity? Reprod 2012;144:153–63. https://doi.org/10.1530/REP-12-0121.
[8] Yeh J, Kim BS, Peresie J, Page C. Declines in levels of hyperpolarization-activated cation (HCN) channels in the rat ovary after cisplatin exposure. Reprod Sci 2009;16:986–94. https://doi.org/10.1177/1933719109339217.
[9] Horicks F, Van Den Steen G, Houben S, Englert Y, Demeestere I. Folliculogenesis is not fully inhibited during GnRH analogues treatment in mice challenging their efficiency to preserve the ovarian reserve during chemotherapy in this model. PLoS ONE 2015;10:e0137164https://doi.org/10.1371/journal.pone.0137164.
[10] Chapman RM, Sutcliffe SB. Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin's disease. Blood 1981;58:849–51.
[11] McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. Endocr Rev 2000;21:200–14. https://doi.org/10.1210/edrv.21.2.0394.
[12] Demeestere I, Streiff AK, Suzuki J, Al-Khabouri S, Mahrous E, Tan SL, et al. Follicle-stimulating hormone accelerates mouse oocyte development in vivo. Biol Reprod 2012;87(3):1–11. https://doi.org/10.1095/biolreprod.112.099929.
[13] Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. Oncologist 2007;12:1044–54. https://doi.org/10.1634/theoncologist.12-9-1044.
[14] Rossi V, Lispi M, Longobardi S, Mattei M, Rella FD, Salustri A, et al. LH prevents cisplatin-induced apoptosis in oocytes and preserves female fertility in mouse. Cell Death Differ 2017;24:72–82. https://doi.org/10.1038/cdd.2016.97.
[15] Sánchez F, Smitz J. Molecular control of oogenesis. Biochim Biophys Acta 2012;1822:1896–912. https://doi.org/10.1016/j.bbadis.2012.05.013.
[16] Su HI, Maas K, Sluss PM, Chang RJ, Hall JE, Joffe H. The impact of depot GnRH agonist on AMH levels in healthy reproductive-aged women. J Clin Endocrinol Metab 2013;98:E1961–6. https://doi.org/10.1210/jc.2013-2410.
[17] Mohamed KA, Davies WaR, Lashen H. Antimüllerian hormone and pituitary gland activity after prolonged down-regulation with goserelin acetate. Fertil Steril 2006;86:1515–7. https://doi.org/10.1016/j.fertnstert.2006.03.047.
[18] Roness H, Gavish Z, Cohen Y, Meirow D. Ovarian follicle burnout: a universal phenomenon? Cell Cycle 2013;12:3245–6. https://doi.org/10.4161/cc.26358.
[19] Hasky N, Uri-Belapolsky S, Goldberg K, Miller I, Grossman H, Stemmer SM, et al. Gonadotrophin-releasing hormone agonists for fertility preservation: unraveling the enigma? Hum Reprod 2015;30:1089–101. https://doi.org/10.1093/humrep/dev037.
[20] Kitajima Y, Endo T, Nagasawa K, Manase K, Honnma H, Baba T, et al. Hyperstimulation and a gonadotropin-releasing hormone agonist modulate ovarian vascular permeability by altering expression of the tight junction protein claudin-5. Endocrinology 2006;147:694–9. https://doi.org/10.1210/en.2005-0700.
[21] Jayaprakasan K, Campbell BK, Hopkisson JF, Clewes JS, Johnson IR, Raine-Fenning NJ. Effect of pituitary desensitization on the early growing follicular cohort estimated using anti-Mullerian hormone. Hum Reprod 2008;23:2577–83. https://doi.org/10.1093/humrep/den282.
[22] Dada T, Salha O, Allgar V, Sharma V. Utero-ovarian blood flow characteristics of pituitary desensitization. Hum Reprod 2001;16:1663–70.
[23] Yu Ng EH, Chi Wai Chan C, Tang OS, Shu Biu Yeung W, Chung Ho P. Effect of pituitary downregulation on antral follicle count, ovarian volume and stromal blood flow measured by three-dimensional ultrasound with power Doppler prior to ovarian stimulation. Hum Reprod 2004;19:2811–5. https://doi.org/10.1093/humrep/deh500.
[24] Ben-Aharon I, Granot T, Meizner I, Hasky N, Tobar A, Rizel S, et al. Long-term follow-up of chemotherapy-induced ovarian failure in young breast cancer patients: the role of vascular toxicity. Oncologist 2015;20:985–91. https://doi.org/10.1634/theoncologist.2015-0044.
[25] Meirow D, Dor J, Kaufman B, Shrim A, Rabinovici J, Schiff E, et al. Cortical fibrosis and blood-vessels damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. Hum Reprod 2007;22:1626–33. https://doi.org/10.1093/humrep/dem027.
[26] Asimakopoulos B, Nikolettos N, Nehls B, Diedrich K, Al-Hasani S, Metzen E. Gonadotropin-releasing hormone antagonists do not influence the secretion of steroid hormones but affect the secretion of vascular endothelial growth factor from human granulosa luteinized cell cultures. Fertil Steril 2006;86:636–41. https://doi.org/10.1016/j.fertnstert.2006.01.046.
[27] Harrison GS, Wierman ME, Nett TM, Glode LM. Gonadotropin-releasing hormone and its receptor in normal and malignant cells. Endocr Relat Cancer 2004;11:725–48. https://doi.org/10.1677/erc.1.00777.
[28] Whitelaw PF, Eidne KA, Sellar R, Smyth CD, Hillier SG. Gonadotropin-releasing hormone receptor messenger ribonucleic acid expression in rat ovary. Endocrinology 1995;136:172–9. https://doi.org/10.1210/endo.136.1.7828528.
[29] Gründker C, Emons G. Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer. Reprod Biol Endocrinol 2003;1:65. https://doi.org/10.1186/1477-7827-1-65.
[30] Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update 2008;14:543–52. https://doi.org/10.1093/humupd/dmn022.
[31] Soleimani R, Heytens E, Oktay K. Enhancement of neoangiogenesis and follicle survival by sphingosine-1-phosphate in human ovarian tissue xenotransplants. PLoS ONE 2011;6:e19475https://doi.org/10.1371/journal.pone.0019475.
[32] Li F, Turan V, Lierman S, Cuvelier C, De Sutter P, Oktay K. Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death. Hum Reprod 2014;29:107–13. https://doi.org/10.1093/humrep/det391.
[33] Morita Y, Perez GI, Paris F, Miranda SR, Ehleiter D, Haimovitz-Friedman A, et al. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. Nat Med 2000;6:1109–14. https://doi.org/10.1038/80442.
[34] Tilly JL, Johnson J. Recent arguments against germ cell renewal in the adult human ovary: is an absence of marker gene expression really acceptable evidence of an absence of oogenesis? Cell Cycle 2007;6:879–83. https://doi.org/10.4161/cc.6.8.4185.
[35] Sobinoff AP, Nixon B, Roman SD, McLaughlin EA. Staying alive: PI3K pathway promotes primordial follicle activation and survival in response to 3MC-induced ovotoxicity. Toxicol Sci 2012;128:258–71. https://doi.org/10.1093/toxsci/kfs137.
[36] Kalich-Philosoph L, Roness H, Carmely A, Fishel-Bartal M, Ligumsky H, Paglin S, et al. Cyclophosphamide triggers follicle activation and "burnout"; AS101 prevents follicle loss and preserves fertility. Sci Transl Med 2013;5:185ra62. https://doi.

org/10.1126/scitranslmed.3005402.
[37] Edwards BS, Isom WJ, Navratil AM. Gonadotropin releasing hormone activation of the mTORC2/Rictor complex regulates actin remodeling and ERK activity in LβT2 cells. Mol Cell Endocrinol 2017;439:346–53. https://doi.org/10.1016/j.mce.2016.09.021.
[38] Ataya KM, McKanna JA, Weintraub AM, Clark MR, LeMaire WJ. A luteinizing hormone-releasing hormone agonist for the prevention of chemotherapy-induced ovarian follicular loss in rats. Cancer Res 1985;45:3651–6.
[39] Ataya KM, Palmer KC, Blacker CM, Moghissi KS, Mohammad SH. Inhibition of rat ovarian [3H]thymidine uptake by luteinizing hormone-releasing hormone agonists: a possible mechanism for preventing damage by cytotoxic agents. Cancer Res 1988;48:7252–6.
[40] Ataya K, Tadros M, Ramahi A. Gonadotropin-releasing hormone agonist inhibits physiologic ovarian follicular loss in rats. Acta Endocrinol 1989;121:55–60.
[41] Bokser L, Szende B, Schally AV. Protective effects of D-Trp6-luteinising hormone-releasing hormone microcapsules against cyclophosphamide-induced gonadotoxicity in female rats. Br J Cancer 1990;61:861–5.
[42] Ataya K, Rao LV, Lawrence E, Kimmel R. Luteinizing hormone-releasing hormone agonist inhibits cyclophosphamide-induced ovarian follicular depletion in rhesus monkeys. Biol Reprod 1995;52:365–72.
[43] Yüce MA, Balkanli Kaplan P, Gücer F, Doğanay L, Altaner S, Canda T, et al. Prevention of cyclophosphamide-induced ovarian damage by concomitant administration of GnRHa in mice: a dose-dependent relationship? Eur J Gynaecol Oncol 2004;25:628–31.
[44] Danforth DR, Arbogast LK, Friedman CI. Acute depletion of murine primordial follicle reserve by gonadotropin-releasing hormone antagonists. Fertil Steril 2005;83:1333–8. https://doi.org/10.1016/j.fertnstert.2004.12.030.
[45] Kishk EAF, Mohammed Ali MH. Effect of a gonadotropin-releasing hormone analogue on cyclophosphamide-induced ovarian toxicity in adult mice. Arch Gynecol Obstet 2013;287:1023–9. https://doi.org/10.1007/s00404-012-2658-y.
[46] Kanter M, Sapmaz-Metin M, Serez B. Effects of GnRHa on early embryonic development in mice receiving cyclophosphamide. Arch Gynecol Obstet 2016;293:203–9. https://doi.org/10.1007/s00404-015-3831-x.
[47] Tan S-J, Yeh Y-C, Shang W-J, Wu G-J, Liu J-Y, Chen C-H. Protective effect of a gonadotropin-releasing hormone analogue on chemotherapeutic agent-induced ovarian gonadotoxicity: a mouse model. Eur J Obstet Gynecol Reprod Biol 2010;149:182–5. https://doi.org/10.1016/j.ejogrb.2009.12.028.
[48] Lin Q, Wang Y, Weng H, Sheng X, Jiang Q, Yang Z. Influence of gonadotropin-releasing hormone agonist on the effect of chemotherapy upon ovarian cancer and the prevention of chemotherapy-induced ovarian damage: an experimental study with nu/nu athymic mice. J Zhejiang Univ Sci 2012;13:894–903. https://doi.org/10.1631/jzus.B1100369.
[49] Zhang Y, Ding JX, Tao X, Lu ZY, Wang JJ, Feng WW, et al. Goserelin can inhibit ovarian cancer proliferation and simultaneously protect ovarian function from cisplatin: an in vitro and in vivo study. J Chemother 2013;25:96–103. https://doi.org/10.1179/1973947813Y.0000000069.
[50] Detti L, Uhlmann RA, Zhang J, Diamond MP, Saed GM, Fletcher NM, et al. Goserelin fosters bone elongation but does not prevent ovarian damage in cyclophosphamide-treated prepubertal mice. Fertil Steril 2014;101(1157–1164):e1https://doi.org/10.1016/j.fertnstert.2013.12.028.
[51] Park I, Lee S, Ryu K-J, Min K-J, Hong JH, Song JY, et al. A gonadotropin-releasing hormone agonist for the prevention of docetaxel-induced gonadal damage. J Obstet Gynaecol 2017;37:783–9. https://doi.org/10.1080/01443615.2017.1306839.
[52] Horicks F, Van Den Steen G, Gervy C, Clarke HJ, Demeestere I. Both in vivo FSH depletion and follicular exposure to Gonadotrophin-releasing hormone analogues in vitro are not effective to prevent follicular depletion during chemotherapy in mice. Mol Hum Reprod 2018;24:221–32. https://doi.org/10.1093/molehr/gay005.
[53] Ataya K, Ramahi-Ataya A. Reproductive performance of female rats treated with cyclophosphamide and/or LHRH agonist. Reprod Toxicol 1993;7:229–35.
[54] Montz FJ, Wolff AJ, Gambone JC. Gonadal protection and fecundity rates in cyclophosphamide-treated rats. Cancer Res 1991;51:2124–6.
[55] Letterie GS. Anovulation in the prevention of cytotoxic-induced follicular attrition and ovarian failure. Hum Reprod 2004;19:831–7. https://doi.org/10.1093/humrep/deh120.
[56] Li Q, Szatmary P, Liu Y, Ding Z, Zhou J, Sun Y, et al. Orthotopic transplantation of cryopreserved mouse ovaries and gonadotrophin releasing hormone analogues in the restoration of function following chemotherapy-induced ovarian damage. PLoS ONE 2015;10:e0120736https://doi.org/10.1371/journal.pone.0120736.
[57] Parlakgumus HA, Kilicdag EB, Bolat FA, Haydardedeoglu B, Parlakgumus A. GNRH agonists and antagonists in rescue for cyclophosphamide-induced ovarian damage: friend or foe? Arch Gynecol Obstet 2015;291:1403–10. https://doi.org/10.1007/s00404-014-3564-2.
[58] Matsuo G, Ushijima K, Shinagawa A, Takahashi S-I, Fujiyoshi N, Takemoto S, et al. GnRH agonist acts as ovarian protection in chemotherapy induced gonadotoxicity: an experiment using a rat model. Kurume Med J 2007;54:25–9.
[59] Li X, Kang X, Deng Q, Cai J, Wang Z. Combination of a GnRH agonist with an antagonist prevents flare-up effects and protects primordial ovarian follicles in the rat ovary from cisplatin-induced toxicity: a controlled experimental animal study. Reprod Biol Endocrinol 2013;11:16. https://doi.org/10.1186/1477-7827-11-16.
[60] Ozcelik B, Turkyilmaz C, Ozgun MT, Serin IS, Batukan C, Ozdamar S, et al. Prevention of paclitaxel and cisplatin induced ovarian damage in rats by a gonadotropin-releasing hormone agonist. Fertil Steril 2010;93:1609–14. https://doi.org/10.1016/j.fertnstert.2009.02.054.
[61] Wang Y, Tian X, Liang L, Wang Y, Wang R, Cheng X, et al. Mechanistic study on triptorelin action in protecting from 5-FU-induced ovarian damage in rats. Oncol Res 2014;22:283–92. https://doi.org/10.3727/096504015X14410238486720.
[62] Knudtson JF, Tellez Santos M, Failor CM, Binkley PA, Venesky JP, Tekmal RR, et al. A combination of a GnRH antagonist and agonist for fertility preservation in an adolescent female murine model. Reprod Sci 2017;24:1280–3. https://doi.org/10.1177/1933719116682876.
[63] Imai A, Sugiyama M, Furui T, Tamaya T, Ohno T. Direct protection by a gonadotropin-releasing hormone analog from doxorubicin-induced granulosa cell damage. Gynecol Obstet Invest 2007;63:102–6. https://doi.org/10.1159/000096062.
[64] Bildik G, Akin N, Senbabaoglu F, Sahin GN, Karahuseyinoglu S, Ince U, et al. GnRH agonist leuprolide acetate does not confer any protection against ovarian damage induced by chemotherapy and radiation in vitro. Hum Reprod 2015;30:2912–25. https://doi.org/10.1093/humrep/dev257.
[65] Jiménez R. Ovarian organogenesis in mammals: mice cannot tell us everything. Sex Dev 2009;3:291–301. https://doi.org/10.1159/000280584.
[66] Matikainen T, Ding YQ, Vergara M, Huhtaniemi I, Couzinet B, Schaison G. Differing responses of plasma bioactive and immunoreactive follicle-stimulating hormone and luteinizing hormone to gonadotropin-releasing hormone antagonist and agonist treatments in postmenopausal women. J Clin Endocrinol Metab 1992;75:820–5. https://doi.org/10.1210/jcem.75.3.1517372.
[67] Horvath JE, Bajo AM, Schally AV, Kovacs M, Herbert F, Groot K. Effects of long-term treatment with the luteinizing hormone-releasing hormone (LHRH) agonist Decapeptyl and the LHRH antagonist Cetrorelix on the levels of pituitary LHRH receptors and their mRNA expression in rats. Proc Natl Acad Sci 2002;99:15048–53. https://doi.org/10.1073/pnas.232579499.
[68] Gosden RG, Rutherford AJ, Norfolk DR. Transmission of malignant cells in ovarian grafts. Hum Reprod 1997;12:403.
[69] Choi D, Lee E, Hwang S, Jun K, Kim D, Yoon BK, et al. The biological significance of phospholipase C beta 1 gene mutation in mouse sperm in the acrosome reaction, fertilization, and embryo development. J Assist Reprod Genet 2001;18:305–10.
[70] Millar RP, Pawson AJ, Morgan K, Rissman EF, Lu Z-L. Diversity of actions of GnRHs mediated by ligand-induced selective signaling. Front Neuroendocrinol 2008;29:17–35. https://doi.org/10.1016/j.yfrne.2007.06.002.
[71] Arora KK, Chung HO, Catt KJ. Influence of a species-specific extracellular amino acid on expression and function of the human gonadotropin-releasing hormone receptor. Mol Endocrinol 1999;13:890–6. https://doi.org/10.1210/mend.13.6.0291.
[72] Choi J-H, Gilks CB, Auersperg N, Leung PCK. Immunolocalization of gonadotropin-releasing hormone (GnRH)-I, GnRH-II, and type I GnRH receptor during follicular development in the human ovary. J Clin Endocrinol Metab 2006;91:4562–70. https://doi.org/10.1210/jc.2006-1147.
[73] Torrealday S, Lalioti MD, Guzeloglu-Kayisli O, Seli E. Characterization of the gonadotropin releasing hormone receptor (GnRHR) expression and activity in the female mouse ovary. Endocrinology 2013;154:3877–87. https://doi.org/10.1210/en.2013-1341.
[74] Li M, Huang H, Liang Y, Tan J, Lin D. Effect of zoladex administered before chemotherapy on menstruation of patients with breast cancer. Chin J Clin Oncol 2008;35:905–7. n.d.
[75] Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril 2009;91:694–7. https://doi.org/10.1016/j.fertnstert.2007.12.044.
[76] Sverrisdottir A, Nystedt M, Johansson H, Fornander T. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. Breast Cancer Res Treat 2009;117:561–7. https://doi.org/10.1007/s10549-009-0313-5.
[77] Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol 2011;29:2334–41. https://doi.org/10.1200/JCO.2010.32.5704.
[78] Sun J, Ren Y, Li W. Effect of zoladex administered before chemotherapy on menstruation of patients with breast cancer. Chin Disab Med 2011;19:15–6. n.d.
[79] Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA 2011;306:269–76. https://doi.org/10.1001/jama.2011.991.
[80] Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. JAMA 2015;314:2632–40. https://doi.org/10.1001/jama.2015.17291.
[81] Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacevic M, Gross-King M, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. J Clin Oncol 2012;30:533–8. https://doi.org/10.1200/JCO.2011.34.6890.
[82] Elgindy EA, El-Haieg DO, Khorshid OM, Ismail EI, Abdelgawad M, Sallam HN, et al. Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial. Obstet Gynecol 2013;121:78–86. https://doi.

org/10.1097/AOG.0b013e31827374e2.
[83] Song G, Gao H, Yuan Z. Effect of leuprolide acetate on ovarian function after cyclophosphamide-doxorubicin-based chemotherapy in premenopausal patients with breast cancer: results from a phase II randomized trial. Med Oncol 2013;30:667. https://doi.org/10.1007/s12032-013-0667-8.
[84] Jiang FY, Zhang QQ, Zeng J. Protective effect of GnRHa on chemotherapy induced ovarian damage in breast cancer patients. Shandong Med J. 2013;53(8):16–8. n.d.
[85] Karimi-Zarchi M, Forat-Yazdi M, Vafaeenasab MR, Nakhaie-Moghadam M, Miratashi-Yazdi A, Teimoori S, et al. Evaluation of the effect of GnRH agonist on menstrual reverse in breast cancer cases treated with cyclophosphamide. Eur J Gynaecol Oncol 2014;35:59–61.
[86] Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015;372:923–32. https://doi.org/10.1056/NEJMoa1413204.
[87] Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Moseley A, et al. Final analysis of the prevention of early menopause study (POEMS)/SWOG intergroup S0230. J Natl Cancer Inst 2018. https://doi.org/10.1093/jnci/djy185.
[88] Leonard RCF, Adamson DJA, Bertelli G, Mansi J, Yellowlees A, Dunlop J, et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol 2017;28:1811–6. https://doi.org/10.1093/annonc/mdx184.
[89] Zhang Y, Ji Y, Li J, Lei L, Wu S, Zuo W, et al. Sequential versus simultaneous use of chemotherapy and gonadotropin-releasing hormone agonist (GnRHa) among estrogen receptor (ER)-positive premenopausal breast cancer patients: effects on ovarian function, disease-free survival, and overall survival. Breast Cancer Res Treat 2018;168:679–86. https://doi.org/10.1007/s10549-018-4660-y.
[90] Rugo HS, Rosen MP. Reducing the long-term effects of chemotherapy in young women with early-stage breast cancer. JAMA 2011;306:312–4. https://doi.org/10.1001/jama.2011.1019.
[91] Regan MM, Walley BA, Francis PA, Fleming GF, Láng I, Gómez HL, et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. Ann Oncol 2017;28:2225–32. https://doi.org/10.1093/annonc/mdx285.
[92] Lambertini M, Goldrat O, Toss A, Azim HA, Peccatori FA, Ignatiadis M, et al. Fertility and pregnancy issues in BRCA-mutated breast cancer patients. Cancer Treat Rev 2017;59:61–70. https://doi.org/10.1016/j.ctrv.2017.07.001.
[93] Peccatori FA, Mangili G, Bergamini A, Filippi F, Martinelli F, Ferrari F, et al. Fertility preservation in women harboring deleterious BRCA mutations: ready for prime time? Hum Reprod 2018;33:181–7. https://doi.org/10.1093/humrep/dex356.
[94] Lambertini M, Goldrat O, Ferreira AR, Dechene J, Azim HA, Desir J, et al. Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. Ann Oncol 2018;29:237–43. https://doi.org/10.1093/annonc/mdx639.
[95] Waxman JH, Ahmed R, Smith D, Wrigley PF, Gregory W, Shalet S, et al. Failure to preserve fertility in patients with Hodgkin's disease. Cancer Chemother Pharmacol 1987;19:159–62.
[96] Giuseppe L, Attilio G, Edoardo DN, Loredana G, Cristina L, Vincenzo L. Ovarian function after cancer treatment in young women affected by Hodgkin disease (HD). Hematol 2007;12:141–7. https://doi.org/10.1080/10245330600954072.
[97] Behringer K, Wildt L, Mueller H, Mattle V, Ganitis P, van den Hoonaard B, et al. No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group. Ann Oncol 2010;21:2052–60. https://doi.org/10.1093/annonc/mdq066.
[98] Demeestere I, Brice P, Peccatori FA, Kentos A, Gaillard I, Zachee P, et al. Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomized trial. J Clin Oncol 2013;31:903–9. https://doi.org/10.1200/JCO.2012.42.8185.
[99] Demeestere I, Brice P, Peccatori FA, Kentos A, Dupuis J, Zachee P, et al. No Evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. J Clin Oncol 2016;34:2568–74. https://doi.org/10.1200/JCO.2015.65.8864.
[100] Gilani MM, Hasanzadeh M, Ghaemmaghami F, Ramazanzadeh F. Ovarian preservation with gonadotropin-releasing hormone analog during chemotherapy. Asia Pac J Clin Oncol 2007;3:79–83. https://doi.org/10.1111/j.1743-7563.2007.00089.x.
[101] Clowse MEB, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. J Womens Health 2002;2009(18):311–9. https://doi.org/10.1089/jwh.2008.0857.
[102] Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. Breast Cancer Res Treat 2010;122:803–11. https://doi.org/10.1007/s10549-010-0996-7.
[103] Kim SS, Lee JR, Jee BC, Suh CS, Kim SH, Ting A, et al. Use of hormonal protection for chemotherapy-induced gonadotoxicity. Clin Obstet Gynecol 2010;53:740–52. https://doi.org/10.1097/GRF.0b013e3181f96cb1.
[104] Bedaiwy MA, Abou-Setta AM, Desai N, Hurd W, Starks D, El-Nashar SA, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. Fertil Steril 2011;95:906–14. https://doi.org/10.1016/j.fertnstert.2010.11.017. e1–e4.
[105] Chen H, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev 2011:CD008018. https://doi.org/10.1002/14651858.CD008018.pub2.
[106] Yang B, Shi W, Yang J, Liu H, Zhao H, Li X, et al. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials. Breast 2013;22:150–7. https://doi.org/10.1016/j.breast.2012.12.008.
[107] Wang C, Chen M, Fu F, Huang M. Gonadotropin-releasing hormone analog cotreatment for the preservation of ovarian function during gonadotoxic chemotherapy for breast cancer: a meta-analysis. PLoS ONE 2013;8:e66360https://doi.org/10.1371/journal.pone.0066360.
[108] Zhang Y, Xiao Z, Wang Y, Luo S, Li X, Li S. Gonadotropin-releasing hormone for preservation of ovarian function during chemotherapy in lymphoma patients of reproductive age: a summary based on 434 patients. PLoS ONE 2013;8:e80444https://doi.org/10.1371/journal.pone.0080444.
[109] Sun X, Dongol S, Jiang J, Kong B. Protection of ovarian function by GnRH agonists during chemotherapy: a meta-analysis. Int J Oncol 2014;44:1335–40. https://doi.org/10.3892/ijo.2014.2296.
[110] Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev 2014;40:675–83. https://doi.org/10.1016/j.ctrv.2013.12.001.
[111] Vitek WS, Shayne M, Hoeger K, Han Y, Messing S, Fung C. Gonadotropin-releasing hormone agonists for the preservation of ovarian function among women with breast cancer who did not use tamoxifen after chemotherapy: a systematic review and meta-analysis. Fertil Steril 2014;102(808–815):e1https://doi.org/10.1016/j.fertnstert.2014.06.003.
[112] Elgindy E, Sibai H, Abdelghani A, Mostafa M. Protecting ovaries during chemotherapy through gonad suppression: a systematic review and meta-analysis. Obstet Gynecol 2015;126:187–95. https://doi.org/10.1097/AOG.0000000000000905.
[113] Shen Y-W, Zhang X-M, Lv M, Chen L, Qin T-J, Wang F, et al. Utility of gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a systematic review and meta-analysis. OncoTargets Ther 2015;8:3349–59. https://doi.org/10.2147/OTT.S95936.
[114] Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol 2015;26:2408–19. https://doi.org/10.1093/annonc/mdv374.
[115] Munhoz RR, Pereira AAL, Sasse AD, Hoff PM, Traina TA, Hudis CA, et al. Gonadotropin-releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early-stage breast cancer: a systematic review and meta-analysis. JAMA Oncol 2016;2:65–73. https://doi.org/10.1001/jamaoncol.2015.3251.
[116] Silva C, Caramelo O, Almeida-Santos T, Ribeiro Rama AC. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-analysis. Hum Reprod 2016;31:2737–49. https://doi.org/10.1093/humrep/dew224.
[117] Bai F, Lu Y, Wu K, Chen Q, Ding L, Ge M, et al. Protecting effects of gonadotropin-releasing hormone agonist on chemotherapy-induced ovarian damage in premenopausal breast cancer patients: a systematic review and meta-analysis. Breast Care 2017;12:48–52. https://doi.org/10.1159/000454983.
[118] Senra JC, Roque M, Talim MCT, Reis FM, Tavares RLC. Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;51:77–86. https://doi.org/10.1002/uog.18934.
[119] Hickman LC, Llarena NC, Valentine LN, Liu X, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a systematic review and meta-analysis of the potential role for gonadotropin-releasing hormone agonists. J Assist Reprod Genet 2018. https://doi.org/10.1007/s10815-018-1128-2.
[120] Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol 2018;36:1981–90. https://doi.org/10.1200/JCO.2018.78.0858.
[121] Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol 2017;29:243–52. https://doi.org/10.1097/CCO.0000000000000380.
[122] Lawrenz B, Fehm T, von Wolff M, Soekler M, Huebner S, Henes J, et al. Reduced pretreatment ovarian reserve in premenopausal female patients with Hodgkin lymphoma or non-Hodgkin-lymphoma–evaluation by using antimüllerian hormone and retrieved oocytes. Fertil Steril 2012;98:141–4. https://doi.org/10.1016/j.fertnstert.2012.04.021.
[123] Lekovich J, Lobel ALS, Stewart JD, Pereira N, Kligman I, Rosenwaks Z. Female

patients with lymphoma demonstrate diminished ovarian reserve even before initiation of chemotherapy when compared with healthy controls and patients with other malignancies. J Assist Reprod Genet 2016;33:657–62. https://doi.org/10.1007/s10815-016-0689-1.

[124] Lambertini M, Demeestere I. Another step towards improving oncofertility counselling of young women with Hodgkin's lymphoma. Lancet Oncol 2018;19:1264–6. https://doi.org/10.1016/S1470-2045(18)30562-X.

[125] Anderson RA, Remedios R, Kirkwood AA, Patrick P, Stevens L, Clifton-Hadley L, et al. Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. Lancet Oncol 2018;19:1328–37. https://doi.org/10.1016/S1470-2045(18)30500-X.

[126] Zhao J, Liu J, Chen K, Li S, Wang Y, Yang Y, et al. What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. Breast Cancer Res Treat 2014;145:113–28. https://doi.org/10.1007/s10549-014-2914-x.

[127] Lambertini M, Campbell C, Bines J, Korde LA, Izquierdo M, Fumagalli D, et al. Adjuvant anti-HER2 therapy, treatment-related amenorrhea, and survival in premenopausal HER2-positive early breast cancer patients. J Natl Cancer Inst 2018. https://doi.org/10.1093/jnci/djy094.

[128] European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, Anderson R, Bartlett J, Braat D, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod 2016;31:926–37. https://doi.org/10.1093/humrep/dew027.