Check for updates

Utility of gonadotropin-releasing hormone agonists for fertility preservation in women receiving chemotherapy: pros and cons

Marie-Madeleine Dolmans, M.D., Ph.D.,[a,b] Hugh S. Taylor, M.D.,[c] Kenny A. Rodriguez-Wallberg, M.D., Ph.D.,[d,e] Zeev Blumenfeld, M.D.,[f] Matteo Lambertini, M.D., Ph.D.,[g,h] Michael von Wolff, M.D.,[i] and Jacques Donnez, M.D., Ph.D.[j,k]

[a] Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium; [b] Gynecology Department, Cliniques Universitaires Saint Luc, Brussels, Belgium; [c] Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut; [d] Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [e] Department of Reproductive Medicine, Division of Gynecology and Reproduction, Karolinska University Hospital, Stockholm, Sweden; [f] Department of Reproductive Endocrinology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [g] Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [h] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy; [i] University Women's Hospital, Bern, Switzerland; [j] Société de Recherche pour l'Infertilité, Brussels, Belgium; and [k] Catholic University of Louvain, Brussels, Belgium

Disclaimer: Authors for "fertile battles" are chosen to represent the full breadth of opinions. Individual authors, even within one side of the debate, do not necessarily agree with all viewpoints expressed.

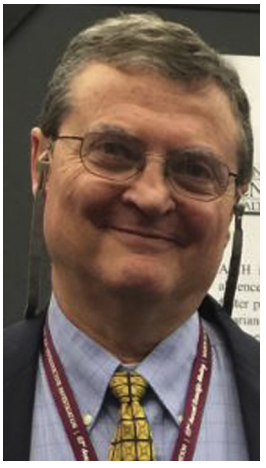


CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy

Con 1: Marie-Madeleine Dolmans, M.D., Ph.D.

Chemotherapy-induced ovarian damage: apoptosis and/or in vitro activation?

The term "ovarian reserve" is typically used to refer to the population of primordial follicles (PMFs) (1). This population is very sensitive to cytotoxic drugs, especially alkylating agents (cyclophosphamide, busulfan, ifosfamide). Among them, cyclophosphamide (CPA) is the alkylating agent that causes the most damage to oocytes and granulosa cells (2). Alkylating-like platinum complexes (such as cisplatin, anthracyclanes [including doxorubicin]) should also be considered as ovo-toxic drugs.



PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy

Pro 1: Zeev Blumenfeld, M.D.

The End of Controversy

More than 50 publications (14 randomized controlled trials [RCTs], 25 non-RCTs, and 20 meta-analyses) and five recent international expert consensus meetings reported more than 3,100 GnRH-a cotreated patients, demonstrating a significant decrease in the premature ovarian insufficiency (POI) rate in survivors of malignant/autoimmune diseases (44–80). Long-term analysis (>5–7 years), in the two main RCTs, validated the evidence that GnRH-a cotreatment significantly decreased POI and

You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/31168

M.M.D. has nothing to disclose. H.S.T. has nothing to disclose. K.A.R.-W. has nothing to disclose. Z.B. has nothing to disclose. M.L. reports advisory role and speaker honoraria from Roche and Novartis; other from Takeda, speaker honoraria from Theramex, Lilly, and Pfizer, outside the submitted work. M.v.W. has nothing to disclose. J.D. reports grants and personal fees from Gedeon Richter Group.

Reprint requests: Jacques Donnez, M.D., Ph.D., Société de Recherche pour l'Infertilité, 1150 Brussels, Belgium (E-mail: jacques.donnez@gmail.com).

https://doi.org/10.1016/j.fertnstert.2020.08.011

Copyright ©2020 American Society for Reproductive Medicine, Published by Elsevier Inc.

CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*

Alkylating agents and platinum complexes work similarly, creating DNA cross-links in replicating cells, which finally cause DNA breaks and ultimately trigger apoptosis. Granulosa cells of growing follicles are highly sensitive to toxic drugs, resulting in their apoptosis, as a major mechanism of many chemotherapy agents. The loss of larger growing follicles is responsible for the significant decrease in antimüllerian hormone (AMH) levels during chemotherapy. AMH produced by growing follicles is thought to have an important inhibitory effect on the rate of PMF activation (3). Inhibitory interactions between neighboring PMFs slowing down the rate of activation were also proposed (4). Gaytan et al. (5) suggested that loss of some PMFs would reduce the inhibitory influence on other PMFs within the cluster.

Chemotherapy drugs can also damage the ovary by inducing PMF activation, leading to the "burn-out" of the PMF (6, 7). Roness et al. (6) suggested that there is an AMH level drop within 12 hours of CPA treatment, then subsequently an increase to twice baseline. This increase is maintained for 14 days post-CPA treatment and it was proposed that this AMH increase was due to an increase of growing follicles due to overactivation of quiescent PMFs (6, 7).

The biochemical pathways that regulate the activation of PMF include growth factors acting through various pathways, such as the PI3K/PTEN/AKT pathway and the Hippo pathway (8–11).

These same pathways are also involved in the process of follicle activation observed early after transplantation of ovarian tissue (the post transplantation "burn-out" effect) (11) and are responsible for the loss of PMFs (12).

According to Spears et al., the AKT pathway (acting via FOXO3a) is modulated by both chemotherapy drugs and protectants (14). However, a very recent work reported by Luan et al. (15) contrasts with the Roness et al. (6) and Kalich-Philosoph et al. (7) reports. Indeed, Luan et al. (15) showed that the numbers of Ki67 positive cells were comparable in PBS and CPA injected 8-week-old mice implying that CPA does not activate PMFs into the growing pool of follicles. They demonstrate in an experimental model that CPA induces the loss of primordial oocytes through apoptosis, leading to oocyte death and depletion of the ovarian reserve and that inhibitors of apoptotic pathway components protect follicles from CPA-induced damage (15). We should bear in mind that chemotherapy drugs can also damage the ovarian stroma and vasculature (16, 17), negatively impacting the ovarian reserve as well as the normal follicle development.

In conclusion, for growing follicles, there is large evidence linking CPA exposure to growing follicle and granulosa cells apoptosis. Concerning the PMF, its pool is clearly negatively affected by CPA exposure; however, from the last studies in human ovaries it is not always clear whether the loss of PMF is due to apoptosis (direct damage) and/or is a result of indirect loss due to accelerated activation (14).

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*

increased the pregnancy rate (PR), with comparable survival (39–42, 81, 82).

Even investigators who previously were opposed to GnRH-a cotreatment have more recently changed their conclusions toward support; they should be applauded for their scientific integrity in changing their former conclusions (36–38, 44, 83). Indeed, a previous opponent group (36) subsequently reported that its use in Hodgkin lymphoma has increased the PR (83), concluding that GnRH-a cotreatment is a "strong, independent, and highly significant predictor of pregnancies" (83).

Although menstrual cycles, gonadotropins, sex hormones, and even antral follicle count (AFC) and AMH are surrogate markers, the gold standard of fertility preservation is PR. Three studies from three continents have shown high PR in survivors, after GnRH-a cotreatment: in Wong et al.'s UK study (84), the PR in survivors was 71%; in the POEMS–SWOG RCT in the United States (42), 88% conceived, versus 66.7% in controls ($P=.03$); and in Israel (55), 58% spontaneously conceived versus 35% in controls ($P=.006$).

Moreover, GnRH-a was also effective in stem cell transplantation (SCT) patients treated with aggressive chemotherapy (85, 86) In the SCT+ GnRH-a−treated patients for hematologic malignancies (lymphomas and leukemias), 38.3% (18 of 47) of the survivors resumed cyclic ovarian function (COF), vs. only 11.1% (4/36) for those who did not receive GnRH-a (85).

One of these patients (SCT+ GnRH-a) spontaneously conceived four times and delivered three healthy neonates despite two (repeated) SCTs and aggressive conditioning chemotherapy in parallel with monthly GnRH-a cotreatment (86).

Five international consensus meetings (87–91), and the Cochrane update (67), support the use of GnRH-a. The only conclusion (out of 10) (www.nccn.org) receiving the highest grading, IA, was that regarding GnRH-a (88). The Italian Association of Medical Oncology (AIOM) has adopted the routine clinical use of GnRH-a during chemotherapy (91). In addition, GnRH-a can effectively prevent chemotherapy-associated menometrorrhagia (45–49). In Italy and Israel, the GnRH-a is subsidized to all young patients facing gonadotoxic chemotherapy.

The disagreement between the supporters of GnRH-a cotreatment and opponents has turned occasionally inflamed (44, 45, 92–97) A raised argument claimed that none of the "GnRH-a PRO" studies were blinded or placebo controlled, and therefore were unacceptable (93). On the other hand, these authors (93) asserted that ovarian cryopreservation should be unequivocally established. How many of the ovarian tissue cryopreservation studies were "blinded or placebo controlled" or RCTs? Why apply a double standard? (44, 45, 92, 93)

Demeestere et al. (98) did not find a difference in the POF rate between the GnRH-a and control groups after 1 year, but at the 2-year follow-up (31), the "…restored ovarian function

CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*



Con 2: Hugh S. Taylor, M.D.

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*

was significantly higher in the GnRH-a group ($P=.049$), confirming results of significantly higher AMH" (1.4 vs. 0.5 ng/mL, $P=.04$) (62). A later follow-up concluded no difference vs. "controls." However, the authors mentioned limitations: a "dropout rate of 50%, and 25% loss of follow-up or data unavailability" (63). Although the original power analysis "mandated the accrual of 157 patients… only 63 were evaluated." Furthermore, five pregnancies occurred in patients with protocol-defined POF of "one FSH >40 U/L," challenging the accuracy of the authors' POF definition. The five spontaneous pregnancies in the "POF patients," small numbers, significantly higher AMH in the GnRH-a group, opposing conclusions at 1-, 2-, and 5-year follow-up, and use of norethisterone/hormonal contraceptives make the conclusions equivocal (31, 98, 99).

Possible causes for contradictory reports are different ages, different timing of ovarian function assessment, and variable gonadotoxicity protocols. Resumption of ovarian function may occur as late as 2 years after chemotherapy; therefore, early assessment at 6 months may underestimate the GnRH-a effect (45–49). Indeed, in one study (38), the number of patients resuming cyclic menstruation at 2 years was significantly higher than those with "two menses at 6 months."

Lymphoma patients are younger, treated with either highly gonadotoxic regimens (conditioning before bone marrow transplantation) or of low gonadotoxicity (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), whereas breast cancer patients are older and treated with intermediate gonadotoxic chemotherapy, possibly explaining the difference (44–46). Including patients up to 45 years of age (45, 46) may also be a diverting parameter, because of the low ovarian reserve after age 40 years.

GnRH-a has been recently integrated in national and international guidelines as a strategy for ovarian function preservation during chemotherapy (24, 99). The updated American Society of Clinical Oncology recommendations state that GnRH-a may be offered to patients for reducing chemotherapy-induced POI in addition to cryopreservation (24). Although none of the fertility preservation methods guarantee unequivocal success in achieving future pregnancy, GnRH-a cotreatment should be offered in addition to cryopreservation of embryos, ova, and ovarian tissue (44–46).



Pro 2: Matteo Lambertini, M.D., Ph.D.

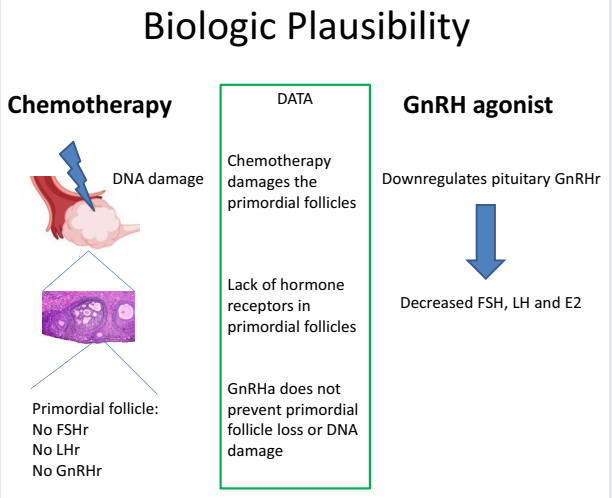
CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*

Role of gonadotropin-releasing hormone in fertility preservation: lack of biological plausibility

The concept of a simple medical treatment that preserves fertility by suppressing ovarian function is appealing; it allows the avoidance of ovarian stimulation/retrieval or surgical intervention to remove oocytes from the adverse effects of gonadotoxic chemotherapy. Unfortunately, suppressing oocyte maturation does not ensure protection of PMFs from toxic exposure. The PMFs consist of an oocyte surrounded by a single layer of flattened granulosa cells and constitute the ovarian reserve. A great majority of these follicles remain dormant throughout most of a woman's life, arrested at prophase I of meiosis. Numerous PMFs resume development each menstrual cycle, independent of gonadotropin stimulation. This follicle activation is irreversible and tightly controlled by not yet fully defined intraovarian signals, not gonadotropins, producing waves of follicular development until menopause. As PMFs are not recruited by gonadotropins, it is not biologically plausible that use of an agent to suppress gonadotropin production would have an impact on the PMF pool.

Histological studies in human ovaries have shown that chemotherapy treatments cause loss of PMFs (18, 19).

FIGURE 1



Chemotherapy damages primordial follicles which do not express gonadotropin-releasing hormone receptors or receptors for follicle-stimulating hormone (FSH) or luteinizing hormone (LH). There is no know biologic mechanism by which gonadotropin-releasing hormone agonists could prevent primordial follicle loss or oocyte DNA damage.

Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*

Lessons from the systematic review of women with early breast cancer

The existence of a hierarchy of evidence is a cornerstone of evidence-based medicine. Systematic reviews and meta-analyses are at the very top of the evidence pyramid, having the chance to provide more reliable answers than single studies by integrating all the relevant data on each specific topic (100). However, despite their potential to be the best source of evidence for informing clinical decision making, they should be well conducted, and specific methodological rules must be followed to avoid misleading results (101, 102).

Probably because of the long-lasting controversy about the role of administering GnRH-a during chemotherapy for preservation of ovarian function and fertility in premenopausal cancer patients (103–105), this topic has been extensively assessed by a large number of systematic reviews and meta-analyses (Table 1) (35, 47, 48, 50–53, 66, 67, 106–118). However, some methodological issues should be considered with some of them that included patients with different tumor types as well as nonrandomized studies, and all but one relied on published data only (103).

One meta-analysis based on individual patient-level data from randomized trials in breast cancer was specifically conducted to try to overcome these important limitations (47). Individual patient-level data were obtained from five major trials: two from the United States (POEMS and Moffitt-led trial) (37, 41, 81), one from Italy (PROMISE-GIM6) (40, 81), one from the United Kingdom (Anglo Celtic Group OPTION) (42), and one from Germany (GBG-37 ZORO) (38). In these studies, 873 patients with a median age of 38 years (interquartile range, 34–42 years) were randomized to receive chemotherapy alone (n = 437) or with concurrent GnRH-a (n = 436) (4). Use of GnRH-a during chemotherapy was associated with a significant reduction (from 30.9% to 14.1%) in the rates of chemotherapy-induced POI (adjusted odds ratio [OR] 0.38, 95% confidence interval [CI] 0.26–0.57). The gonadal-protective effect of GnRH-a administration was observed irrespectively of patients' age at the time of treatment (including among premenopausal women >40 years of age at diagnosis), hormone receptor status (including in the case of hormone receptor–positive breast cancer), as well as type and duration of chemotherapy. By pooling the results of the three trials reporting on this outcome (41, 42, 81), a higher number of patients (37 vs. 20) treated with GnRH-a during chemotherapy had a posttreatment pregnancy (incidence rate ratio 1.83, 95% CI 1.06–3.15). All the pregnancies were observed in patients less than 40 years of age at the time of diagnosis and the majority (86.0%) in those with hormone receptor–negative breast cancer.

A major criticism raised regarding this meta-analysis was the impossibility of collecting individual patient-level data

print & web 4C/FPO

CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*

Oktem and Oktay and others have shown that gonadotoxic chemotherapy destroys ovarian germ cells by inducing severe DNA damage both in women and in murine models (20–22). Women treated with alkylating regimens have significantly lower counts of PMFs when compared with those receiving nonalkylating agents or no chemotherapy (23). Chemotherapy regimens, especially those containing alkylating agents, result in significant loss of ovarian reserve by destroying PMFs. Oktay et al. (24) also showed that gonadotropin-releasing hormone agonists (GnRH-a) coadministration did not prevent chemotherapy-induced PMF DNA damage and cell death in a murine model.

GnRH-a desensitize and decrease the numbers of pituitary GnRH receptors resulting in greatly diminished follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the pituitary. Because PMFs do not express FSH, LH, or GnRH receptors, GnRH-a cannot directly affect these follicles or ovarian reserve (Fig. 1) (25). Loss of the small numbers of maturing primary, preantral, or antral follicles would not have a long-term impact on ovarian reserve. However, it has been hypothesized that GnRH-a may still antagonize the cytotoxicity of chemotherapeutics through unknown mechanisms. If true, this effect would not be confined to the ovary and would likely also inhibit the activity of chemotherapy on cancers. Fortunately, GnRH-a does not appear to reduce the effectiveness of chemotherapy. There is no evidence that GnRH antagonists have a direct effect on PMFs.

AMH is perhaps the most widely used marker of ovarian reserve. AMH is produced by the preantral and small antral follicles. AMH inhibits recruitment of follicles from the resting pool during the process of folliculogenesis and selection of the dominant follicle. As a product of active granulosa cells, and not the PMF, AMH can serve only as an indirect marker of ovarian reserve. Although AMH may give some reassurance of folliculogenesis, it cannot directly evaluate the number of PMFs in the ovarian reserve or accurately predict pregnancy. Furthermore, it does not account for the detrimental effects of DNA damage on the oocyte itself that may further limit fertility. AMH is diminished after chemotherapy but may underestimate the full extent of damage to ovarian reserve after chemotherapy.

In summary, there is no biologically plausible theory that would justify administration of GnRH antagonists for the protection of the hormone-insensitive PMF. The best way to protect the PMF from damage is to remove it from the exposure using assisted reproductive technology and oocyte retrieval or by surgical tissue removal for future transplantation (26, 27). This point of view is reflected in the most recent American Society for Clinical Oncology Clinical Practice Guidelines (24). GnRH-a should not be used in place of proven fertility preservation methods.

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*

from all the randomized trials and the small numbers of posttreatment pregnancies observed (93). However, results are similar to and consistent with to those reported in the largest meta-analysis based on abstracted data that included 1,231 breast cancer patients from 12 trials (48). Moreover, it should be noted that none of the randomized trials investigating the role of temporary ovarian suppression with GnRH-a during chemotherapy were designed or powered to observe differences in posttreatment pregnancies (on the contrary, PR was a preplanned secondary endpoint only in one study); desire for a future pregnancy was not an inclusion criterion in these trials; and the follow-up time available in the majority of the trials was too short to assess this important outcome (103, 119).

Globally, two main lessons derive from this individual patient-level data meta-analysis. First, temporary ovarian suppression with GnRH-a during chemotherapy should now be considered a standard option for ovarian function preservation in premenopausal breast cancer patients, as currently recommended by several guidelines (24, 90, 91, 120, 121). Irrespective of pregnancy desire and patient age, preventing the negative consequences of POI represents another important goal for many premenopausal women with newly diagnosed breast cancer (122–125). Second, considering that the data on posttreatment pregnancies remain limited (especially among patients with hormone receptor–positive disease that are candidates to adjuvant endocrine therapy following chemotherapy) (126), use of GnRH-a during cytotoxic treatment should not be considered a stand-alone fertility-preserving procedure alternative to cryopreservation options. Nevertheless, the observed significant result in posttreatment pregnancies favoring GnRH-a administration should not be denied. Hence, this strategy can also be offered to increase the chances of natural conception following cryopreservation techniques, as well as to those patients without access to assisted reproductive technology options. Collecting long-term follow-up information from the available randomized trials should be highly encouraged in order to provide more reliable evidence on the actual fertility preservation potential of temporary ovarian suppression with GnRH-a during chemotherapy.

CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*



Con 3: Kenny A. Rodriguez-Wallberg, M.D., Ph.D.

Concerns about methodology and interpretation of the data presented in clinical trials and meta-analyses

When meta-analyses collide, a final answer is unlikely to be found. There are several reasons for such collisions, including the obvious methodological pitfalls; but in general, it is well understood that the overall conclusions derived from a meta-analysis will depend on the quality of the studies included (28). To date, data of a substantial number of women receiving GnRH-a during treatment for cancer or autoimmune diseases in clinical trials have been meta-analyzed. However, results have sometimes collided.

What are the possible reasons for this discrepancy? First, it is important to highlight that sound investigations of efficacious fertility preservation methods in women treated for cancer or autoimmune diseases are complicated. As the proportion of women from the cohort who will wish to become pregnant or who will attempt pregnancy is unknown, the a priori population needed for such a study, using the most relevant fertility outcomes for the women in this setting, the livebirth rate, is likely not feasible. A possible illustration for this is the summary of two recent well-powered clinical trials regarding assisted reproductive technology (ART) treatment in cohorts of women in which every individual in the study would attempt pregnancy (29, 30). In the first study, a predefined expected livebirth rate of 35%, based on previous data, indicated the need to randomize 1,150 women. The number was not achieved, and, additionally troublesome, the actual livebirth rate obtained in the study was lower than the rate anticipated in the sample size calculation (29). The second trial found no beneficial effect of endometrial scratching in ART treatments (30). In that study, the needed number of women was achieved, with an actual successful randomization of 1,364 women and well-powered results supporting the inefficacy of the intervention investigated (30).

Many investigators have considered recovery of menses after chemotherapy treatment—or the opposite, treatment-induced amenorrhea—as sufficient clinical surrogates for fertility. Unfortunately, the surrogates chosen have not been uniformly predefined and have differed across studies, affecting the power calculations and resulting in

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*



Pro 3: Michael von Wolff, M.D.

For patients, the overall clinical effect is more important than the effect in specific diseases and the understanding of the molecular effects

There are various approaches to the development of pharmaceuticals. In most cases, a drug is developed based on a known molecular mechanism. It is also possible that drugs are tested for another indication based on pathophysiological considerations without a clearly known molecular pathophysiological mechanism.

The latter was the case with GnRH-a. GnRH-a were, among other things, developed for the purpose of suppressing the pituitary—ovarian axis. Building on the hypothesis that a suppressed ovary is less susceptible to chemotherapy, GnRH-a were suggested and tested as a possible fertility protective agent (56).

After several years of controversy, the result is sufficiently well known: in breast cancer, GnRH-a reduce the risk of amenorrhea in the short term (47) and in the long term (81), and increase the chance of a later pregnancy (47) (see Lambertini's contribution in this article).

So, the question can be asked: Are the results of these studies enough to allow GnRH-a to be used as a fertility protective agent during gonadotoxic treatment for any tumor entities?

The answer is a clear "yes and no": "yes" because it must be assumed that a therapy that has a fertility-protective effect in breast cancer should also be effective for malignancies treated with other chemotherapy; and "no" because we are no longer in the Middle Ages, and therefore any indication should be evidence based.

The clinically most relevant question is: How good is the evidence beyond breast cancer?

GnRH-a are also used for Hodgkin lymphoma. In contrast to breast cancer, no short-term effect on the amenorrhea rate and thus no fertility-protective effect has been observed in Hodgkin lymphoma (51). However, the total number of subjects in the prospective randomized studies (GnRH-a, 53; without GnRH-a, 56) and the number of women with a significantly reduced ovarian reserve/amenorrhea (GnRH-a, 10; without GnRH-a, 18) was very low.

In addition, in contrast to breast cancer, no long-term effect could be determined. Demeestere et al. (31) examined 67

CON: GnRH-a should not be used for fertility preservation in women receiving chemotherapy *(continued)*

heterogeneous outcomes. Investigators have reported pregnancies at variable follow-up, sometimes as short as 12 months (Table 2), raising questions concerning how long we should wait for pregnancies to occur, as it is not expected that women would attempt a pregnancy soon after the completion of cancer treatment.

Why is this important? A favor for higher PR in women who have received GnRH-a has not been confirmed in the only well-powered randomized controlled study with sufficient long-term follow-up (31). Even considering that a long follow-up period could improve the quality of studies designed to capture clinical outcomes, current data indicate that only a minority, between 10% and 20% of women accessing fertility preservation, seek care after the completion of cancer treatment to attempt pregnancy (32–34). Hence, most women might not attempt pregnancy in the future. For this reason, there is a need to find further appropriate surrogate outcomes for female fertility potential and to make these studies feasible.

What about using AMH as biochemical marker of ovarian reserve? The idea has been around for several years. However, the biomarker has been included as a surrogate endpoint in only a minority of studies (Table 2). Some of these studies have also been included in a meta-analysis, which did not find any protective effects of GnRH-a in AMH levels (35).

The question of ovarian protection through GnRH-a is fascinating from a researcher's point of view. In some meta-analyses, important studies have been left out. All randomized controlled studies performed have been unblinded; thus all women knew whether or not they had received GnRH-a. This bias is reflected in the higher pregnancy attempts reported in some major trials (43), which may explain the higher number of pregnancies in some of the studies' GnRH-a groups.

PRO: GnRH-a should be used for fertility preservation in women receiving chemotherapy *(continued)*

lymphoma patients with a median follow-up of about 5.5 years and, based especially on the serum FSH concentration, found no long-term fertility-protective effect.

There has been much speculation about the reasons for the different effects of GnRH-a in breast cancer and Hodgkin lymphoma. Are they based on different chemotherapy compositions, on different gonadotoxicities, or are they due to differences in ovarian function that are expressed as a lower ovarian reserve in Hodgkin lymphoma (127); or are the Hodgkin lymphoma study groups simply wrongly selected or too small?Ultimately, we do not know, and further studies will show whether there is really a reason for the differences in both diseases.

Until then, the pragmatic approach should be taken. That is, to combine all studies into an overall meta-analysis and not to differentiate between different tumor entities. The Cochrane analysis from 2019 follows exactly this approach, combining 12 prospective randomized trials of women with breast cancer, ovarian cancer, and Hodgkin lymphoma (25). A summary of the studies found a protective effect of GnRH-a on the maintenance of ovarian function (incidence of menstruation at a follow-up of 12 months). The relative risk for maintaining ovarian function was 1.60 (95% CI 1.14−2.24).

But how can the fertility-protective effect of GnRH-a be explained?Blumenfeld and von Wolff proposed the concept of GnRH-a breaking a pathophysiological vicious cycle (13). This concept states that the chemotherapy-induced destruction of primary and secondary follicles massively increases follicle recruitment through the decrease in AMH and the increase in follicle stimulating hormone leading to the activation and growth of many follicles. GnRH-a could interfere in this mechanism of "follicular burn-out" by reducing FSH release. Although this concept appears attractive at first and could possibly be at least partially effective, it seems to be insufficient to explain the effect of GnRH-a.

Alternatively, the effect of GnRH-a may be based on its effects at the molecular level. Scaruffi et al. found that GnRH-a inhibits the cyclophosphamide-induced and BAX-mediated apoptotic pathway of granulosa cells in human cell-oocyte complexes (128).

In conclusion, the indication for GnRH-a as a fertility-protective measure should be made generously, because there is evidence for a fertility-protective effect. There are first concepts of a molecular mechanism of action; GnRH-a have hardly any side effects; GnRH-a have other advantageous objective effects such as the reduction of severe vaginal bleeding during chemotherapy (129), and, finally, their use has subjective effects such as providing patients with the reassuring certainty that they have done something for their fertility.With a generous indication for the use of GnRH-a, the Hippocratic phrase is still fulfilled, "Primum non nocere, secundum cavere, tertium sanare."

TABLE 1

Available meta-analyses assessing the role of temporary ovarian suppression with GnRH-a during chemotherapy in cancer patients

Author(s), year (reference)	Disease type	No. of included studies (no. of RCTs)	No. of patients	Overall results
Clowse et al., 2009	Autoimmune diseases, HL and NHL	9 (2)	366	Protection for POI
Ben-Aharon et al., 2010	Autoimmune diseases, breast cancer, HL and NHL	16 (5)	681	Protection for POI (not in RCTs)
Kim et al., 2010	Autoimmune diseases, breast cancer, HL and NHL	11 (3)	654	Protection for POI
Bedaiwy et al., 2011	Breast cancer, ovarian cancer, and HL	6 (6)	340	Protection for POI (not for pregnancy)
Yang et al., 2013	Breast cancer	5 (5)	528	Protection for POI (not for pregnancy)
Wang et al., 2013	Breast cancer	7 (7)	677	Protection for POI
Zhang et al., 2013	HL and NHL	7 (3)	434	Protection for POI (not for pregnancy)
Sun et al., 2014	Breast cancer, ovarian cancer, and HL	8 (8)	621	Protection for POI (not for pregnancy)
Del Mastro et al., 2014	Breast cancer, ovarian cancer, HL and NHL	9 (9)	765	Protection for POI
Vitek et al., 2014	Breast cancer (hormone receptor-negative only)	4 (4)	252	No protection
Elgindy et al., 2015	Breast cancer, ovarian cancer, HL and NHL	10 (10)	907	No protection
Shen et al., 2015	Breast cancer	11 (11)	1,062	Protection for POI (not for pregnancy)
Lambertini et al., 2015	Breast cancer	12 (12)	1,231	Protection for POI (also for pregnancy)
Munhoz et al., 2016	Breast cancer	7 (7)	856	Protection for POI (also for pregnancy)
Silva et al., 2016	Breast cancer	7 (7)[a]	1,002[a]	Protection for POI
Bai et al., 2017	Breast cancer	15 (15)[a]	1,540[a]	Protection for POI (also for pregnancy)
Senra et al., 2018	Breast cancer, HL, and NHL	13 (13)	1,208	Protection for POI (also for pregnancy)
Hickman et al., 2018	Breast cancer, ovarian cancer, HL, and NHL	10 (10)	1,051	Protection for POI
Lambertini et al., 2018	Breast cancer	5 (5)[b]	873	Protection for POI (also for pregnancy)
Sofiyeva et al., 2019	Autoimmune diseases, breast cancer, HL, and NHL	18 (11)	1,043	Protection for POI
Zheng et al., 2019	Breast cancer, HL, and NHL	12 (12)	1,413	Protection for POI (not for pregnancy)
Chen et al., 2019	Breast cancer, ovarian cancer, and HL	12 (12)	1,369	Protection for POI (not for pregnancy)

Note: Updated and modified from Lambertini et al. (103).GnRH-a = gonadotropin-releasing hormone agonist; HL = Hodgkin lymphoma; NHL= non-Hodgkin lymphoma; POI = premature ovarian insufficiency; RCT = randomized controlled trial.

[a] Data from the two publications of the PROMISE-GIM6 trial, by Del Mastro et al. (40) and Lambertini et al. (81), were considered twice instead of as from the same study.

[b] Based on individual patient-level data.

Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.

TABLE 2

Data on biochemical markers of ovarian reserve from randomized controlled trials investigating GnRH-a co-treatment during chemotherapy in women treated for cancer

Cancer type	Author(s), year (reference)	Ovarian marker studied	Protective effect in ovarian markers Yes/No	Study size, follow-up duration, and results with regard to markers of ovarian reserve and pregnancies reported
Hodgkin lymphoma	Behringer et al., 2010 (36)	AMH, FSH, estradiol, Inhibin	No	Clinical trial. A priori assumption of 70% protection rate for GnRH-a. 23 Women enrolled. Study follow-up 6, 12, and 18 mo. Ovarian reserve preservation rate was found to be 0%, and study was prematurely closed. No pregnancies occurred during follow-up.

Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.

REFERENCES

1. Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS One 2010;5:e8772.
2. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001;7:535–43.
3. Durlinger AL, Kramer P, Karels B, de Jong FH, Uilenbroek JT, Grootegoed JA, Themmen AP. Control of primordial follicle recruitment

TABLE 2

Continued.

Cancer type	Author(s), year (reference)	Ovarian marker studied	Protective effect in ovarian markers Yes/No	Study size, follow-up duration, and results with regard to markers of ovarian reserve and pregnancies reported
Breast cancer	Munster et al., 2012 (37)	Inhibin A and B, FSH	No	Clinical trial. Planned for 124 patients using an expected amenorrhea rate of 10% in GnRH-a group, compared to 30% in control group and 5-y follow-up. Study stopped for futility after 49 enrolled subjects. At 18-mo follow-up, two women had conceived naturally in the control group, compared to none in GnRH-a group.
Breast cancer, ER neg	Gerber et al., 2011 (38)	AMH, Inhibin B, estradiol, FSH, AFC	No	Clinical trial. Multicenter. 60 Women randomized, 56 completed the study. Follow-up at 4 years for AMH and Inhibin. Marked reduction of AMH and suggested decrease in ovarian function in almost all patients at 2-y follow-up, despite restoration of menstruation. Two pregnancies reported, one in each arm.
Breast cancer, ER neg	Elgindy et al., 2011 (39)	AMH, FSH, LH, estradiol, AFC	No	Clinical trial. Multicenter. 100 Patients randomized. Follow-up at 6, 12, and 18 mo. Ovarian markers reduced similarly in both arms.
Breast cancer	Del Mastro et al., 2011 (40)	No sensitive ovarian markers were investigated, but estradiol and FSH were randomly assessed and reported	FSH and E2 levels were not available in about 30% of patients	Clinical trial. Multicenter. Estimated 280 women needed after assumption of a 60% rate of early menopause in the control group and power to detect a 20% absolute reduction in early menopause in GnRH-a co-treatment group. 282 Women enrolled and 260 evaluated at 12-mo follow-up. Four pregnancies reported, three in GnRH-a and one in control group.

Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.

by anti-Müllerian hormone in the mouse ovary. Endocrinology 1999;140:5789–96.
4. Da Silva-Buttkus P, Marcelli G, Franks S, Stark J, Hardy K. Inferring biological mechanisms from spatial analysis: prediction of a local inhibitor in the ovary. Proc Natl Acad Sci U S A 2009;106:456–61.
5. Gaytan F, Morales C, Leon S, Garcia-Galiano D, Roa J, Tena-Sempere M. Crowding and follicular fate: spatial determinants of follicular reserve and activation of follicular growth in the mammalian ovary. PLoS One 2015;10:e0144099.
6. Roness H, Kashi O, Meirow D. Prevention of chemotherapy-induced ovarian damage. Fertil Steril 2016;105:20–9.
7. Kalich-Philosoph L, Roness H, Carmely A, Fishel-Bartal M, Ligumsky H, Paglin S, et al. Cyclophosphamide triggers follicle activation and

TABLE 2

Continued.

Cancer type	Author(s), year (reference)	Ovarian marker studied	Protective effect in ovarian markers Yes/No	Study size, follow-up duration, and results with regard to markers of ovarian reserve and pregnancies reported
Breast cancer	Moore et al., 2015 (41)	FSH, estradiol, and Inhibin at year 1 and 2 were included as endpoints, but not reported	Inhibin, E2 and FSH were not reported	Clinical trial. Multicenter. Study originally powered for 416 patients by year 2. Reported on 218. More women attempted pregnancy in the GnRH-a group vs controls. At 5-year follow-up, 18 children had been born in the GnRH-a group and 12 in the control group. No data as to whether pregnancies were achieved through ART.
Lymphoma	Demeestere et al., 2016 (31)	AMH, FSH	No	Clinical trial. Multicenter. Estimated 157 women needed on the basis of an assumed 40% difference of chemotherapy-induced ovarian failure between arms. Enrollment was stopped after 129 randomized women, due to similar ovarian failure rates between groups. AMH at 2–4 y and 5–7 y decreased similarly in both arms. During the 7-y follow-up, 17/32 and 15/35 women conceived in the GnRH-a and control groups, respectively, without significant statistical differences between groups.
Breast cancer	Leonard et al., 2017 (42)	AMH, FSH, LH, randomly assessed	No	Clinical trial. Multicenter. Study powered for 250 patients on basis of an expected 20% reduction of rate of premature menopause in GnRH-a group. Analysis reported on 202 patients. No significant differences in AMH found at 3, 12, or 24 mo.

Note: A few studies have reported on pregnancies achieved during follow-up. All studies were unblinded. Follow-up has been variable among studies, with the longest follow-up reported in the study by Demeestere et al. (31). Antimüllerian hormone has been used systematically as a marker of ovarian reserve across the studies. None of the randomized studies investigating changes in ovarian markers associated with chemotherapy found a beneficial effect of GnRH-a co-treatment. AMH = antimüllerian hormone; ART = assisted reproductive technology; ER = estrogen receptor; FSH = follicle-stimulating hormone; GnRH-a = gonadotropin-releasing hormone agonist; LH = luteinizing hormone; neg = negative.

Dolmans. GnRH agonists and fertility preservation. Fertil Steril 2020.

"burnout"; AS101 prevents follicle loss and preserves fertility. Sci Transl Med 2013;5:185ra62.
8. Kawamura K, Cheng Y, Suzuki N, Deguchi M, Sato Y, Takae S, et al. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci U S A 2013;110:17474–9.
9. Grosbois J, Demeestere I. Dynamics of PI3K and Hippo signaling pathways during in vitro human follicle activation. Hum Reprod 2018;33:1705–14.
10. Masciangelo R, Hossay C, Donnez J, Dolmans MM. Does the Akt pathway play a role in follicle activation after grafting of human ovarian tissue? Reprod Biomed Online 2019;39:196–8.
11. Masciangelo R, Hossay C, Chiti MC, Manavella DD, Amorim CA, Donnez J, et al. Role of the PI3K and Hippo pathways in follicle activation after grafting of human ovarian tissue. J Assist Reprod Genet 2020;37:101–8.
12. Dolmans MM, Martinez-Madrid B, Gadisseux E, Guiot Y, Yuan WY, Torre A, et al. Short-term transplantation of isolated human ovarian follicles and cortical tissue into nude mice. Reproduction 2007;134:253–62.
13. Blumenfeld Z, von Wolff M. GnRH analogues and oral contraceptives for fertility preservation during chemotherapy. Hum Reprod Update 2008; 14:543–52.
14. Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA, et al. Ovarian damage from chemotherapy and current approaches to its protection. Hum Reprod Update 2019;25:673–93.
15. Luan Y, Edmonds ME, Woodruff TK, Kim SY. Inhibitors of apoptosis protect the ovarian reserve from cyclophosphamide. J Endocrinol 2019;240:243–56.
16. Oktem O, Oktay K. A novel ovarian xenografting model to characterize the impact of chemotherapy agents on human primordial follicle reserve. Cancer Res 2007;67:10159–62.
17. 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.
18. Familiari G, Caggiati A, Nottola SA, Ermini M, Di Benedetto MR, Motta PM. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. Hum Reprod 1993;8:2080–7.
19. Himelstein-Braw R, Peters H, Faber M. Morphological study of the ovaries of leukaemic children. Br J Cancer 1978;38:82–7.
20. Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer 2007; 110:2222–9.
21. Soleimani R, Heytens E, Darzynkiewicz Z, Oktay K. Mechanisms of chemotherapy-induced human ovarian aging: double-strand DNA breaks and microvascular compromise. Aging 2011;3:782–93.
22. Zymanska KJ, Tan X, Oktay K. Unraveling the mechanisms of chemotherapy-induced damage to human primordial follicle reserve: road to developing therapeutics for fertility preservation and reversing ovarian aging. Mol Hum Reprod 2020;26:553–66.
23. Oktay K, Taylan E, Sugishita Y. Failure of goserelin to prevent chemotherapy- induced damage to ovarian reserve. Cancer Res 2018;78(Suppl), PD7-07.
24. 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;36:1994–2001.
25. Oktay K, Briggs D, Gosden RG. Ontogeny of follicle-stimulating hormone receptor gene expression in isolated human ovarian follicles. J Clin Endocrinol Metab 1997;82:3748–51.
26. Donnez J, Dolmans M. Fertility preservation in women. N Engl J Med 2017; 377:1657–65.
27. Donnez J, Dolmans MM, Diaz C, Pellicer A. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril 2015;104:1097–8.
28. De Vrieze J. The metawars: meta-analyses were supposed to end scientific debates–often, they only cause more controversy. Science 2018;361: 1184–8.
29. Groenewoud ER, Cohlen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJ, de Bruin JP, et al. A randomized controlled, non-inferiority trial of modified natural versus artificial cycle for cryo-thawed embryo transfer. Hum Reprod 2016;31:1483–92.
30. Lensen S, Osavlyuk D, Armstrong S, Stadelmann C, Hennes A, Nappier E, et al. A randomized trial of endometrial scratching before in vitro fertilization. N Engl J Med 2019;380:325–34.
31. 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.
32. Cobo A, Garcia-Velasco J, Domingo J, Pellicer A, Remohi J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod 2018;33:2222–31.
33. Moravek MB, Confino R, Smith KN, Kazer RR, Klock SC, Lawson AK, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril 2018;109:349–55.
34. Marklund A, Eloranta S, Wikander I, Kitlinski ML, Lood M, Nedstrand E, et al. Efficacy and safety of controlled ovarian stimulation using GnRH antagonist protocols for emergency fertility preservation in young women with breast cancer–a prospective nationwide Swedish multicenter study. Hum Reprod 2020;35:929–38.
35. 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.
36. 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.
37. 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.
38. Gerber B, von Minckwitz G, Stehle H, Reiner T, Felderbaum 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.
39. 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.
40. 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.
41. Moore HC, Unger JM, Phillips KA, 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.
42. 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.
43. Oktay K, Rodriguez-Wallberg K, Munster P. Ovarian protection during adjuvant chemotherapy. N Engl J Med 2015;372:2268–9.
44. Blumenfeld Z. Fertility preservation by endocrine suppression of ovarian function using gonadotropin-releasing hormone agonists: the end of the controversy? J Clin Oncol 2018;36:1895–7.
45. Blumenfeld Z. Fertility preservation using GnRH agonists: rationale, possible mechanisms, and explanation of controversy. Clin Med Insights Reprod Health 2019;13, 1179558119870163.
46. Blumenfeld Z, Katz G, Evron A. "An ounce of prevention is worth a pound of cure": the case for and against GnRH-agonist for fertility preservation. Ann Oncol 2014;25:1719–28.
47. 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.

48. 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.
49. Lambertini M, Ginsburg ES, Partridge AH. Update on fertility preservation in young women undergoing breast cancer and ovarian cancer therapy. Curr Opin Obstet Gynecol 2015;27:98–107.
50. 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.
51. 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.
52. 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.
53. 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 Edinb Scotl 2013;22:150–7.
54. Blumenfeld Z, Evron A. Endocrine prevention of chemotherapy-induced ovarian failure. Curr Opin Obstet Gynecol 2016;28:223–9.
55. Blumenfeld Z, Zur H, Dann EJ. Gonadotropin-releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. Oncologist 2015;20:1283–9.
56. Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update 2008;14:543–52.
57. Blumenfeld Z. Chemotherapy and fertility. Best Pract Res Clin Obstet Gynaecol 2012;26:379–90.
58. Blumenfeld Z, Dann E, Avivi I, Epelbaum R, Rowe JM. Fertility after treatment for Hodgkin's disease. Ann Oncol 2002;13(Suppl 1):138–47.
59. Blumenfeld Z, Avivi I, Ritter M, Rowe JM. Preservation of fertility and ovarian function and minimizing chemotherapy-induced gonadotoxicity in young women. J Soc Gynecol Investig 1999;6:229–39.
60. 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.
61. Blumenfeld Z, Avivi I, Eckman A, Epelbaum R, Rowe JM, Dann EJ. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. Fertil Steril 2008;89:166–73.
62. Blumenfeld Z. GnRH-agonists in fertility preservation. Curr Opin Endocrinol Diabetes Obes 2008;15:523–8.
63. Blumenfeld Z, Evron A. Preserving fertility when choosing chemotherapy regimens–the role of gonadotropin-releasing hormone agonists. Expert Opin Pharmacother 2015;16:1009–20.
64. Blumenfeld Z. Pregnancy rate and preservation of cyclic ovarian function with gonadotropin-releasing hormone agonist cotreatment during chemotherapy. JAMA Oncol 2016;2:545–6.
65. Blumenfeld Z. Preservation of ovarian function and fertility despite gonadotoxic chemotherapy. Expert Rev Endocrinol Metab 2012;7:567–76.
66. 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.
67. Chen H, Xiao L, Li J, Cui L, Huang W. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev 2019;3:CD008018.
68. Del Mastro L, Giraudi S, Levaggi A, Pronzato P. Medical approaches to preservation of fertility in female cancer patients. Expert Opin Pharmacother 2011;12:387–96.
69. Pereyra Pacheco B, Méndez Ribas JM, Milone G, Fernández I, Kvicala R, Mila T, et al. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. Gynecol Oncol 2001;81:391–7.
70. Castelo-Branco C, Nomdedeu B, Camus A, Mercadal S, Martínez de Osaba MJ, Balasch J. Use of gonadotropin-releasing hormone agonists in patients with Hodgkin's disease for preservation of ovarian function and reduction of gonadotoxicity related to chemotherapy. Fertil Steril 2007;87:702–5.
71. 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). Hematology 2007;12:141–7.
72. Falorio S, Angrilli F, Fioritoni G. Gonadotropin-releasing hormone analog treatment for the prevention of treatment-related ovarian failure and infertility in women of reproductive age with Hodgkin lymphoma. Leuk Lymphoma 2008;49:1087–93.
73. Huser M, Crha I, Ventruba P, Hudecek R, Zakova J, Smardova L, et al. Prevention of ovarian function damage by a GnRH analogue during chemotherapy in Hodgkin lymphoma patients. Hum Reprod 2008;23:863–8.
74. Urruticoechea A, Arnedos M, Walsh G, Dowsett M, Smith IE. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). Breast Cancer Res Treat 2008;110:411–6.
75. Fox KR, Scialla J, Moore H. Preventing chemotherapy-related amenorrhea using leuprolide during adjuvant chemotherapy for early-stage breast cancer. Proc Am Soc Clin Oncol 2003;22:13.
76. Maisano R, Caristi N, Mare M, Bottari M, Adamo V, Mafodda A, et al. Protective effect of leuprolide on ovarian function in young women treated with adjuvant chemotherapy for early breast cancer: a multicenter phase II study. J Chemother 2008;20:740–3.
77. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum 2005;52:2761–7.
78. Blumenfeld Z, Mischari O, Schultz N, Boulman N, Balbir-Gurman A. Gonadotropin releasing hormone agonists may minimize cyclophosphamide associated gonadotoxicity in SLE and autoimmune diseases. Semin Arthritis Rheum 2011;41:346–52.
79. Liang L, Qiu Q, Yang X, Xu H, Ye Y, Zhan Z, et al. [Role of gonadotropin releasing hormone analogues for ovarian protection in systemic lupus erythematosus patients treated with cyclophosphamide]. Zhonghua Yi Xue Za Zhi 2008;88:1009–11.
80. Henes M, Henes JC, Neunhoeffer E, Von Wolff M, Schmalzing M, Kötter I, et al. Fertility preservation methods in young women with systemic lupus erythematosus prior to cytotoxic therapy: experiences from the FertiPROTEKT network. Lupus 2012;21:953–8.
81. 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.
82. 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 2019;111:210–3.
83. Behringer K, Thielen I, Mueller H, Goergen H, Eibl AD, Rosenbrock J, et al. Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial. Ann Oncol 2012;23:1818–25.
84. Wong M, O'Neill S, Walsh G, Smith IE. Goserelin with chemotherapy to preserve ovarian function in pre-menopausal women with early breast cancer: menstruation and pregnancy outcomes. Ann Oncol 2013;24:133–8.
85. Blumenfeld Z, Patel B, Leiba R, Zuckerman T. Gonadotropin-releasing hormone agonist may minimize premature ovarian failure in young women undergoing autologous stem cell transplantation. Fertil Steril 2012;98:1266–70.

86. Blumenfeld Z, Zuckerman T. Repeated spontaneous pregnancies and successful deliveries after repeated autologous stem cell transplantation and GnRH-agonist treatment. Oncologist 2010;15:59–60.
87. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies–improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533–46.
88. 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.
89. Paluch-Shimon S, Pagani O, Partridge AH, Bar-Meir E, Fallowfield L, Fenlon D, et al. Second international consensus guidelines for breast cancer in young women (BCY2). Breast Edinb Scotl 2016;26:87–99.
90. 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 Edinb Scotl 2017;35:203–17.
91. 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.
92. Oktay K, Turan V. Failure of ovarian suppression with gonadotropin-releasing hormone analogs to preserve fertility: an assessment based on the quality of evidence. JAMA Oncol 2016;2:74–5.
93. Turan V, Bedoschi G, Rodriguez-Wallberg K, Sonmezer M, Pacheco FS, Oktem O, et al. Utility of gonadotropin-releasing hormone agonists for fertility preservation: lack of biologic basis and the need to prioritize proven methods. J Clin Oncol 2019;37:84–6.
94. Blumenfeld Z. Reply to V. Turan et al. J Clin Oncol 2019;37:88–9.
95. Blumenfeld Z. Ovarian tissue transplantation and leukemia. Fertil Steril 2018;109:69–70.
96. Blumenfeld Z. Fertility preservation in leukemia. Oncologist 2018;23:645–6.
97. Blumenfeld Z. ZORO study: discrepancy between the conclusion and the results. J Clin Oncol 2011;29:3340, author reply 3341–2.
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.
99. Condorelli M, Lambertini M, Del Mastro L, Boccardo F, Demeestere I, Bober SL. Fertility, sexuality and cancer in young adult women. Curr Opin Oncol 2019;31:259–67.
100. Berlin JA, Golub RM. Meta-analysis as evidence: building a better pyramid. JAMA 2014;312:603–5.
101. Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. JAMA 2014;312:623–30.
102. Murad MH, Montori VM, Ioannidis JPA, Jaeschke R, Devereaux PJ, Prasad K, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. JAMA 2014;312:171–9.
103. Lambertini M, Horicks F, Del Mastro L, Partridge AH, Demeestere I. Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: from biological evidence to clinical application. Cancer Treat Rev 2019;72:65–77.
104. Lambertini M, Richard F, Nguyen B, Viglietti G, Villarreal-Garza C. Ovarian function and fertility preservation in breast cancer: should gonadotropin-releasing hormone agonist be administered to all premenopausal patients receiving chemotherapy? Clin Med Insights Reprod Health 2019;13, 1179558119828393.
105. Poggio F, Lambertini M, Bighin C, Conte B, Blondeaux E, D'Alonzo A, et al. Potential mechanisms of ovarian protection with gonadotropin-releasing hormone agonist in breast cancer patients: a review. Clin Med Insights Reprod Health 2019;13, 1179558119864584.
106. 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 2009;18:311–9.
107. 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.
108. 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.
109. 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.
110. 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:e66360.
111. 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:e80444.
112. 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.
113. 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;102:808–15.
114. 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.
115. 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.
116. 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;35:571–81.
117. Sofiyeva N, Siepmann T, Barlinn K, Seli E, Ata B. Gonadotropin-releasing hormone analogs for gonadal protection during gonadotoxic chemotherapy: a systematic review and meta-analysis. Reprod Sci 2019;26:939–53.
118. Zheng F, Zhu B, Feng Q, Wu L, Cui Y, Liu Y, et al. Protective effect of gonadotropin-releasing hormone agonist against chemotherapy-induced ovarian dysfunction: a meta-analysis. Oncol Lett 2019;17:5319–26.
119. Lambertini M, Partridge AH, Del Mastro L. Reply to V. Turan et al. J Clin Oncol 2019;37:86–8.
120. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus guidelines for the primary therapy of early breast cancer 2019. Ann Oncol 2019;30:1541–57.
121. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1194–220.
122. 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.
123. Lambertini M, Fontana V, Massarotti C, Poggio F, Dellepiane C, Iacono G, et al. Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: results of the pilot phase of the PREgnancy and FERtility (PREFER) study. Breast 2018;41:51–6.
124. Massarotti C, Scaruffi P, Lambertini M, Sozzi F, Remorgida V, Anserini P. Beyond fertility preservation: role of the oncofertility unit in the reproductive and gynecological follow-up of young cancer patients. Hum Reprod 2019;34:1462–9.

125. Ferreira AR, Di Meglio A, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S, et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. Ann Oncol 2019;30:1784–95.
126. Lambertini M, Blondeaux E, Perrone F, Del Mastro L. Improving adjuvant endocrine treatment tailoring in premenopausal women with hormone receptor-positive breast cancer. J Clin Oncol 2020;38:1258–67.
127. von Wolff M, Bruckner T, Strowitzki T, Germeyer A. Fertility preservation: ovarian response to freeze oocytes is not affected by different malignant diseases–an analysis of 992 stimulations. J Assist Reprod Genet 2018;35:1713–9.
128. Scaruffi P, Stigliani S, Cardinali B, Massarotti C, Lambertini M, Sozzi F, et al. Gonadotropin releasing hormone agonists have an anti-apoptotic effect on cumulus cells. Int J Mol Sci 2019;20:6045.
129. Meirow D, Rabinovici J, Katz D, Or R, Shufaro Y, Ben-Yehuda D. Prevention of severe menorrhagia in oncology patients with treatment-induced thrombocytopenia by luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate. Cancer 2006;107:1634–41.