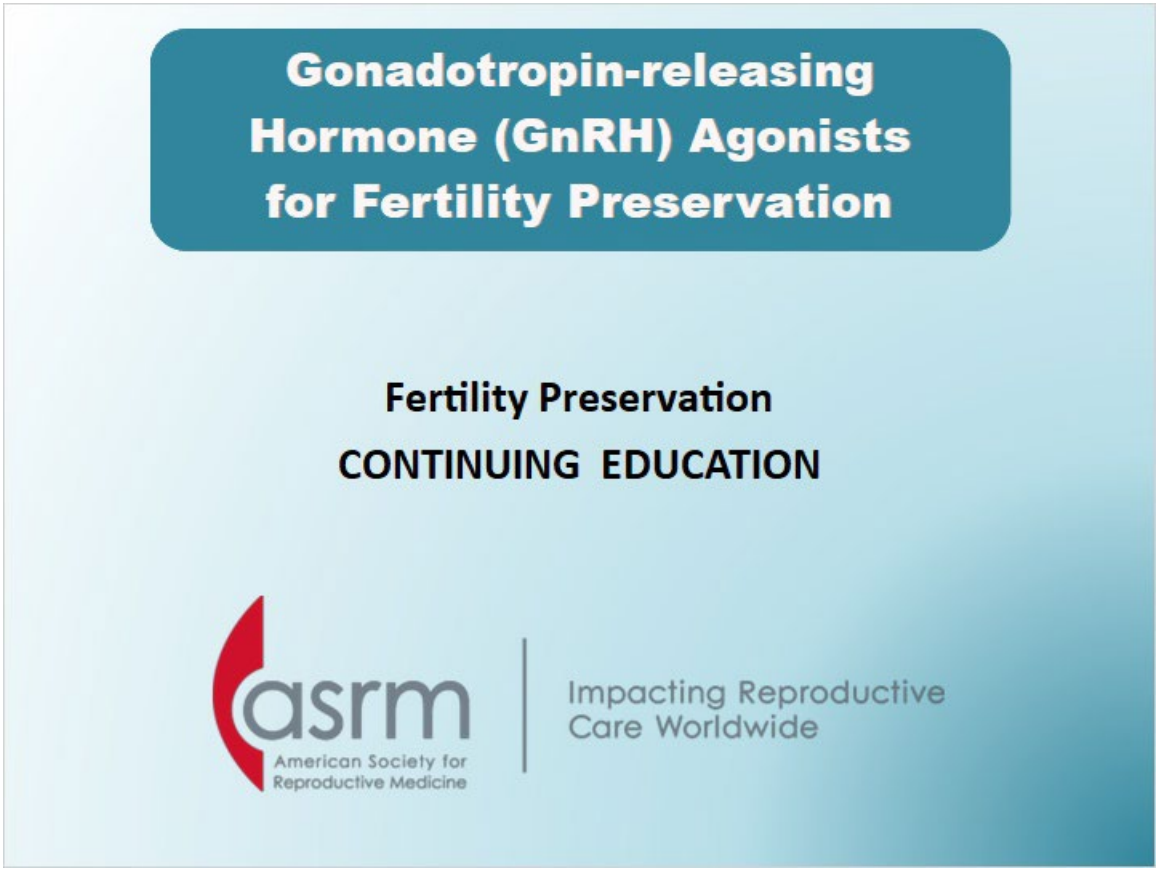
MD120 Lesson 7

1. MD120_L7

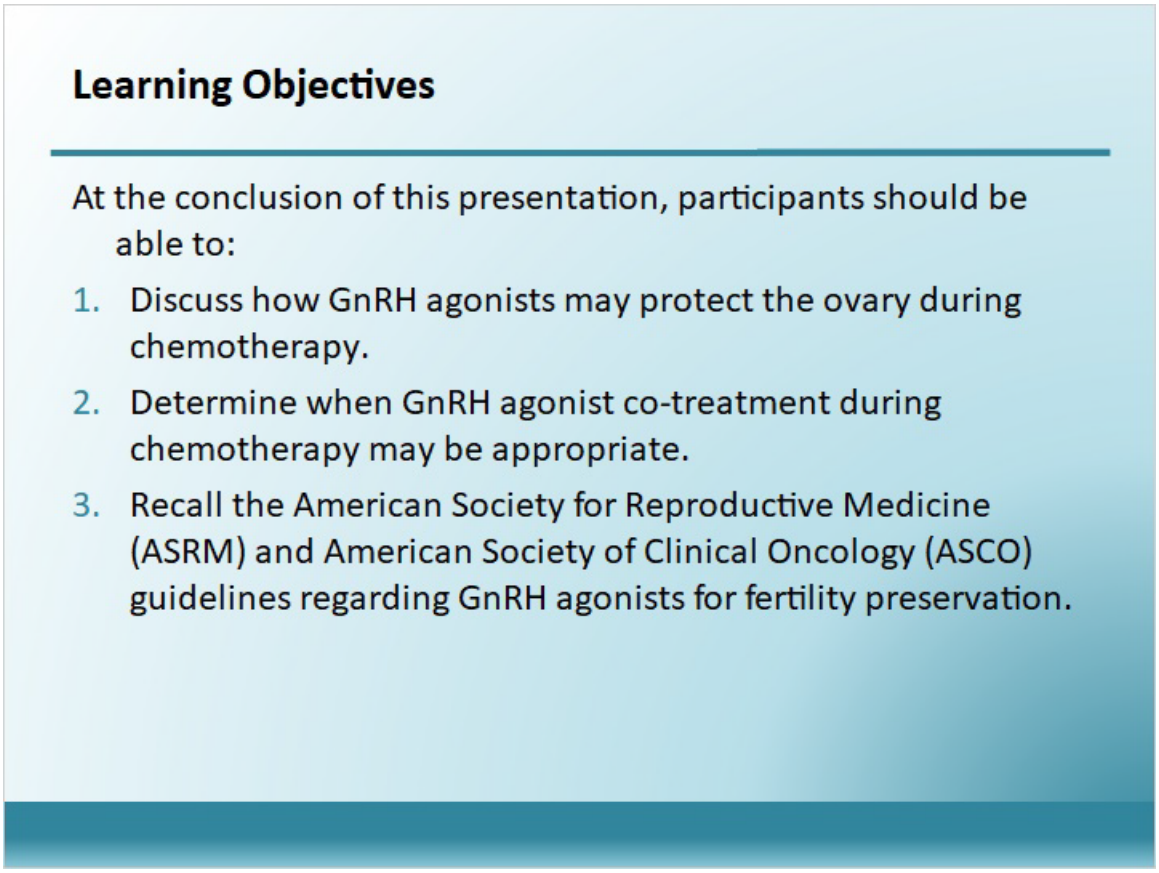
1.1 Gonadotropin-releasing Hormone (GnRH) Agonists for Fertility Preservation



Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Gonadotropin-releasing hormone (GnRH) agonists for fertility preservation."

1.2 Learning Objectives

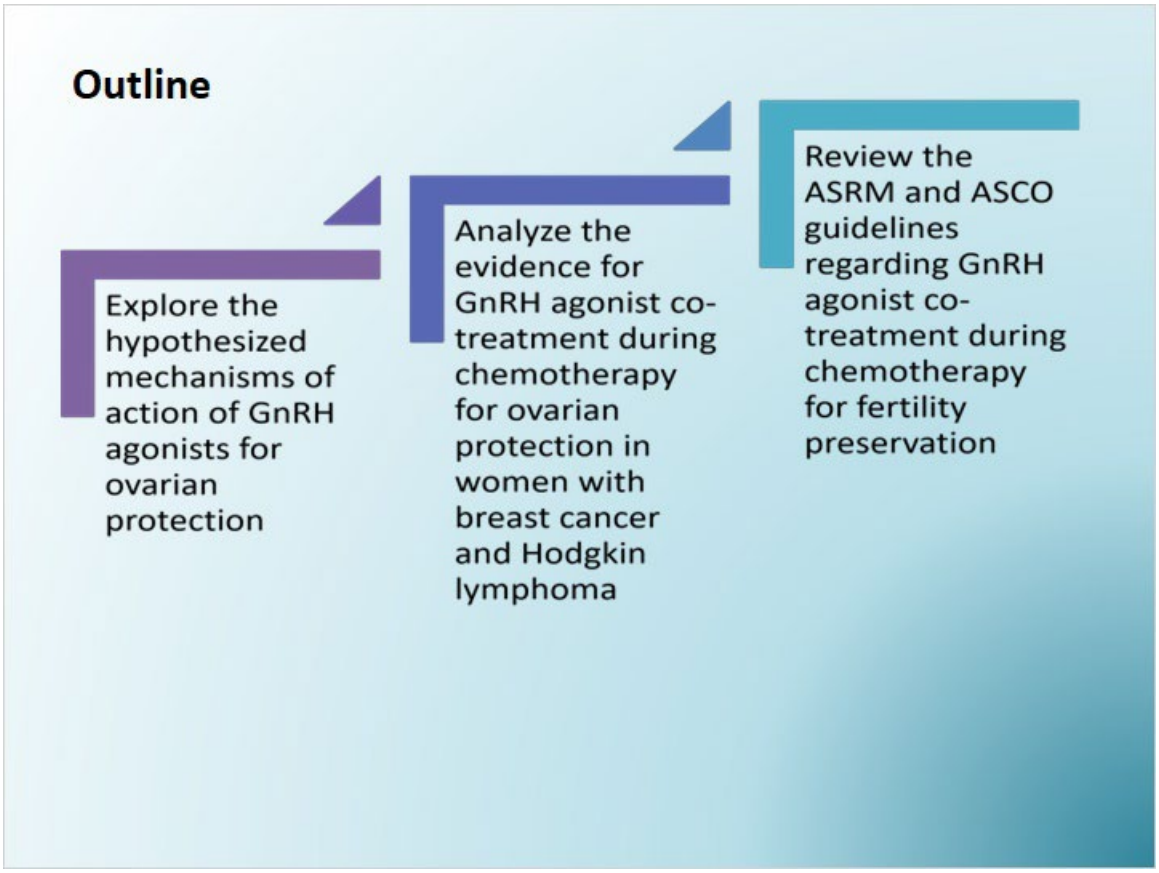


Notes:

At the conclusion of this presentation, participants should be able to:

Discuss the physiology by which GnRH agonists may protect the ovary during chemotherapy.
Determine when GnRH agonist co-treatment during chemotherapy may be appropriate.
Recall the American Society for Reproductive Medicine and American Society of Clinical Oncology guidelines regarding GnRH agonists for fertility preservation.

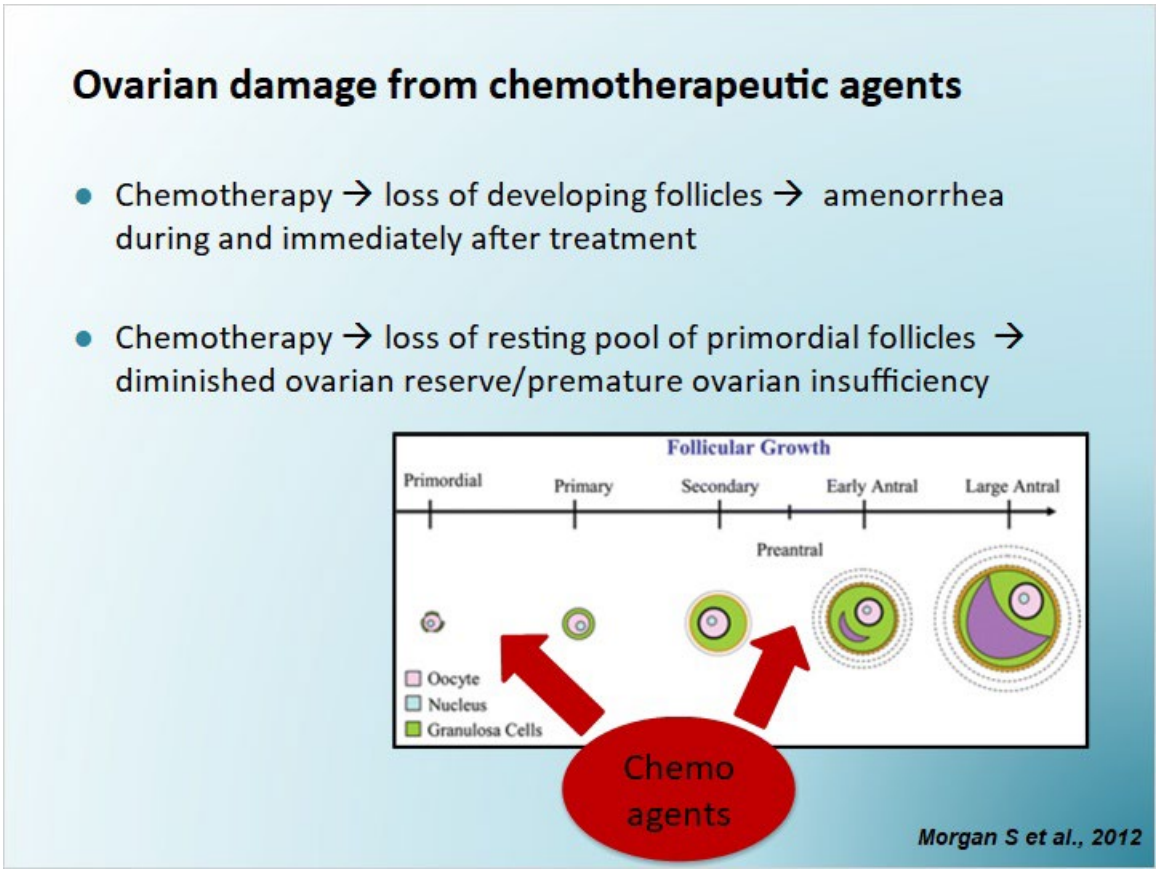
1.3 Outline



Notes:

This presentation will begin by exploring the hypothesized mechanisms of action of GnRH agonists for ovarian protection. Next, the presentation will analyze the evidence for GnRH agonist co-treatment during chemotherapy for ovarian protection in women with breast cancer and Hodgkin lymphoma. This will provide a basis for understanding the ASRM and ASCO guidelines regarding GnRH agonist co-treatment during chemotherapy for fertility preservation.

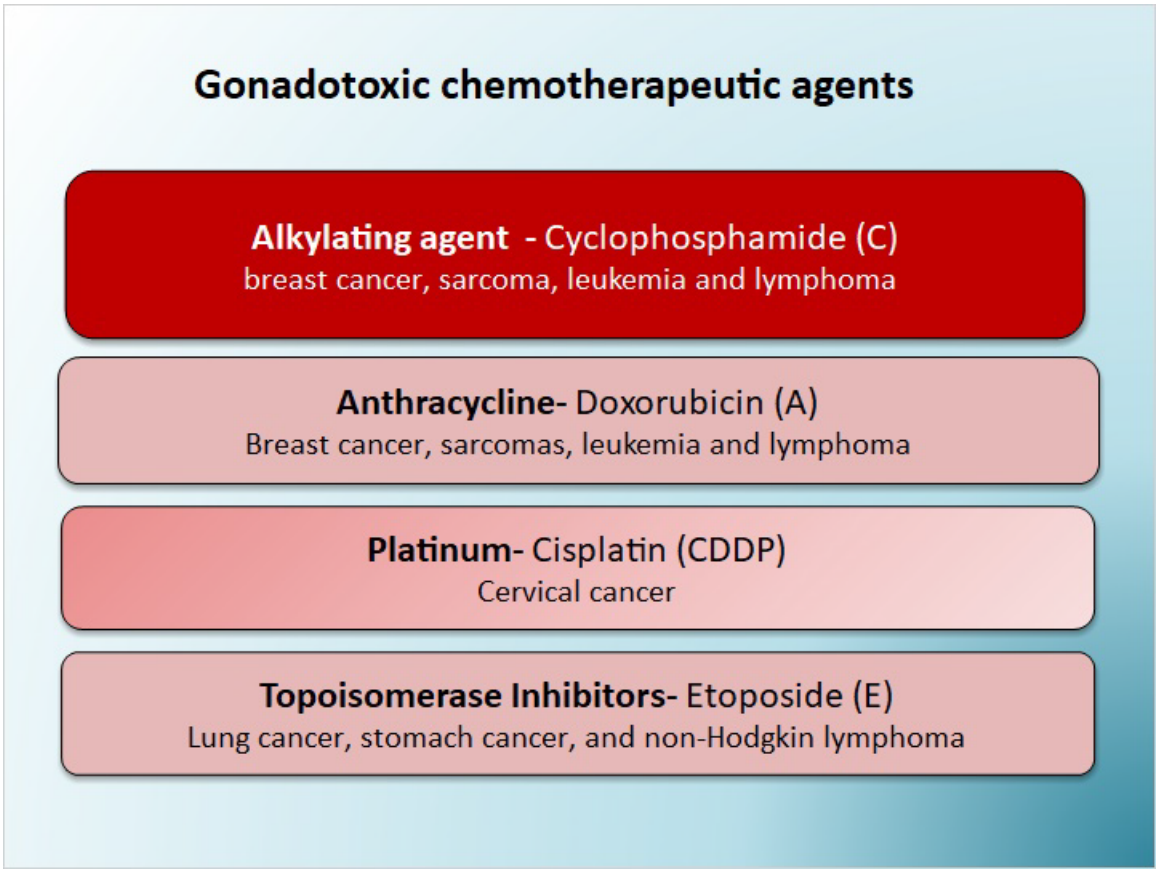
1.4 Ovarian damage from chemotherapeutic agents



Notes:

Chemotherapeutic agents can directly affect the resting pool of primordial follicles and the developing follicle population. A decrease or absence of developing follicles can lead to acute amenorrhea during and immediately post chemotherapy. As growing follicles inhibit the recruitment of primordial follicles, the loss of this population will lead to an increased activation of primordial follicles and the loss of ovarian reserve. This could result in diminished ovarian reserve and premature ovarian insufficiency.

1.5 Gonadotoxic chemotherapeutic agents



Notes:

Let's review the gonadotoxicity of common chemotherapeutic agents.

Cyclophosphamide is an alkylating agent that is used to treat breast cancer, sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and chronic lymphocytic leukemia. It results in intra-strand and inter-strand cross-linking of DNA, which interferes with cell division. It likely targets metabolically active granulosa cells in the ovary. It is depicted as red as it can be highly gonadotoxic at high doses in older women.

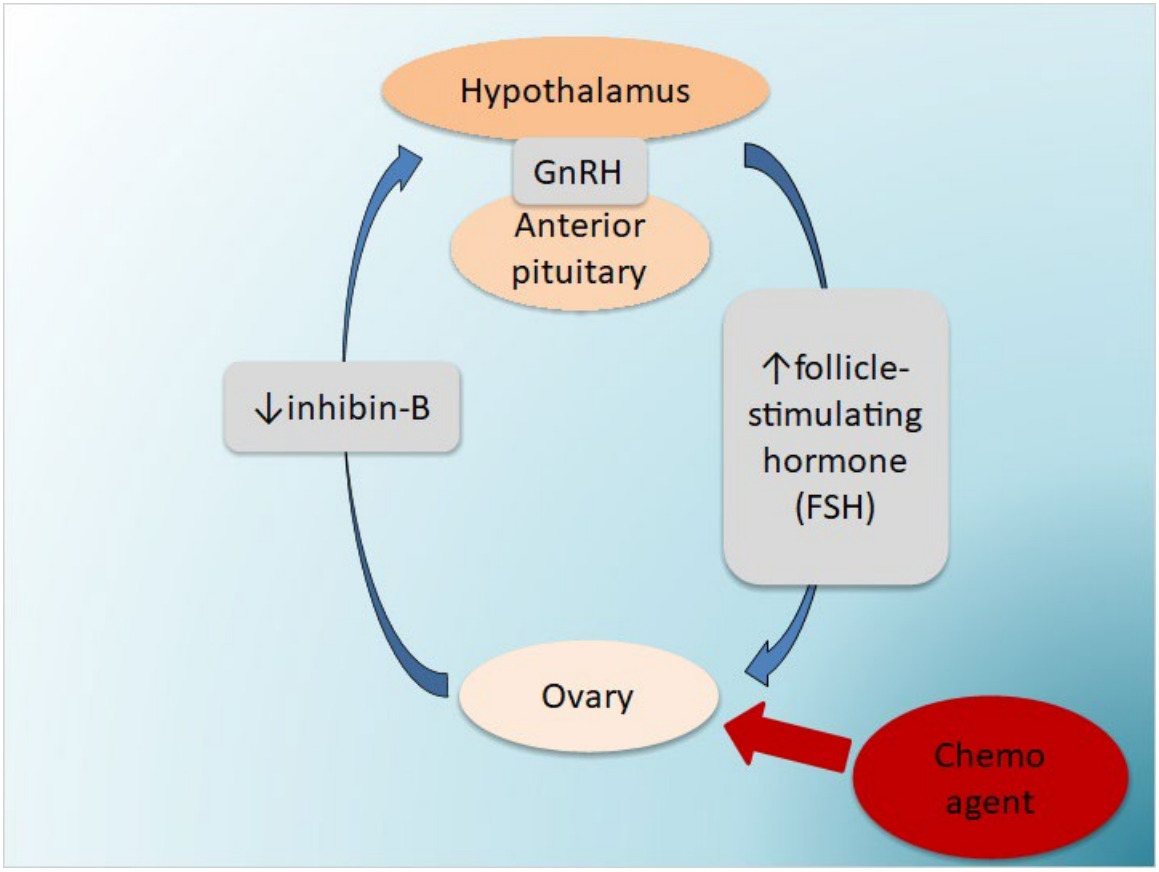
Doxorubicin is an anthracycline which is often used to treat breast cancer, sarcomas, leukemia and lymphomas. Its precise mechanism of action is unclear, though it is thought to intercalate DNA and prevent its replication and transcription, partly through inhibition of topoisomerase II. It likely targets metabolically active granulosa cells in the ovary. It is depicted in pink as it is moderately gonadotoxic.

Cisplatin is a platinum-containing compound that is used to treat cervical cancer. Cisplatin causes DNA damage by the formation of inter-strand and intra-strand DNA adducts. These adducts interfere with cellular transcription and replication. Cisplatin may preferentially target the oocyte and possibly the metabolically active granulosa cells. It is depicted in pink as it is

moderately gonadotoxic.

Etoposide is a topoisomerase II inhibitor which is used to treat lung cancer, stomach cancer, and non-Hodgkin lymphoma. The enzyme topoisomerase allows DNA to unwind during DNA replication, which is blocked by these inhibitors. The primary action in the ovary is likely to be on the proliferating granulosa cells, but these agents may also target the oocytes by inducing double strand DNA breaks which trigger apoptosis. It is depicted in pink as it is moderately gonadotoxic.

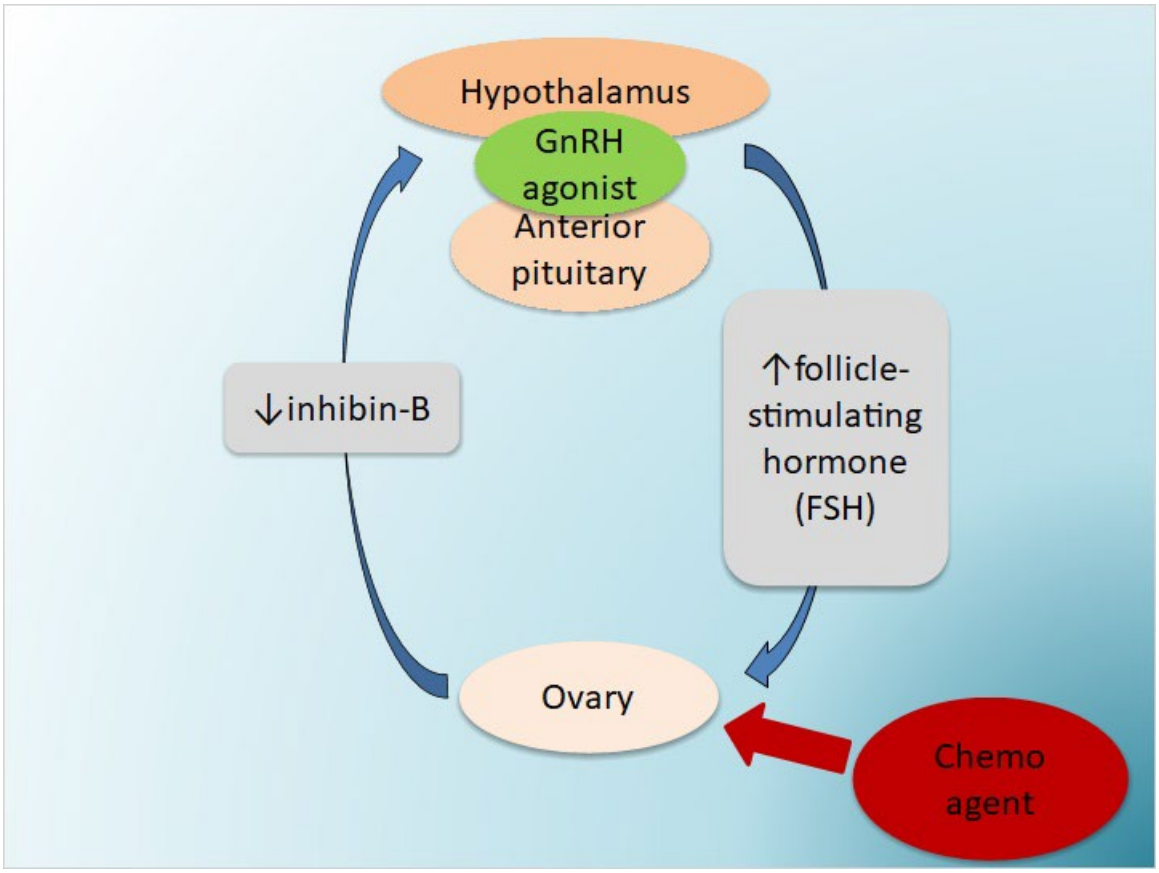
1.6 Untitled Slide



Notes:

The loss of growing follicles induced by these gonadotoxic chemotherapeutic agents will result in less negative feedback by inhibin-B. With less negative feedback, the anterior pituitary increases follicle stimulating hormone (FSH), which increases follicular recruitment. This leads to more follicles being exposed to gonadotoxic chemotherapeutic agents and a persistent cycle of accelerated follicular loss.

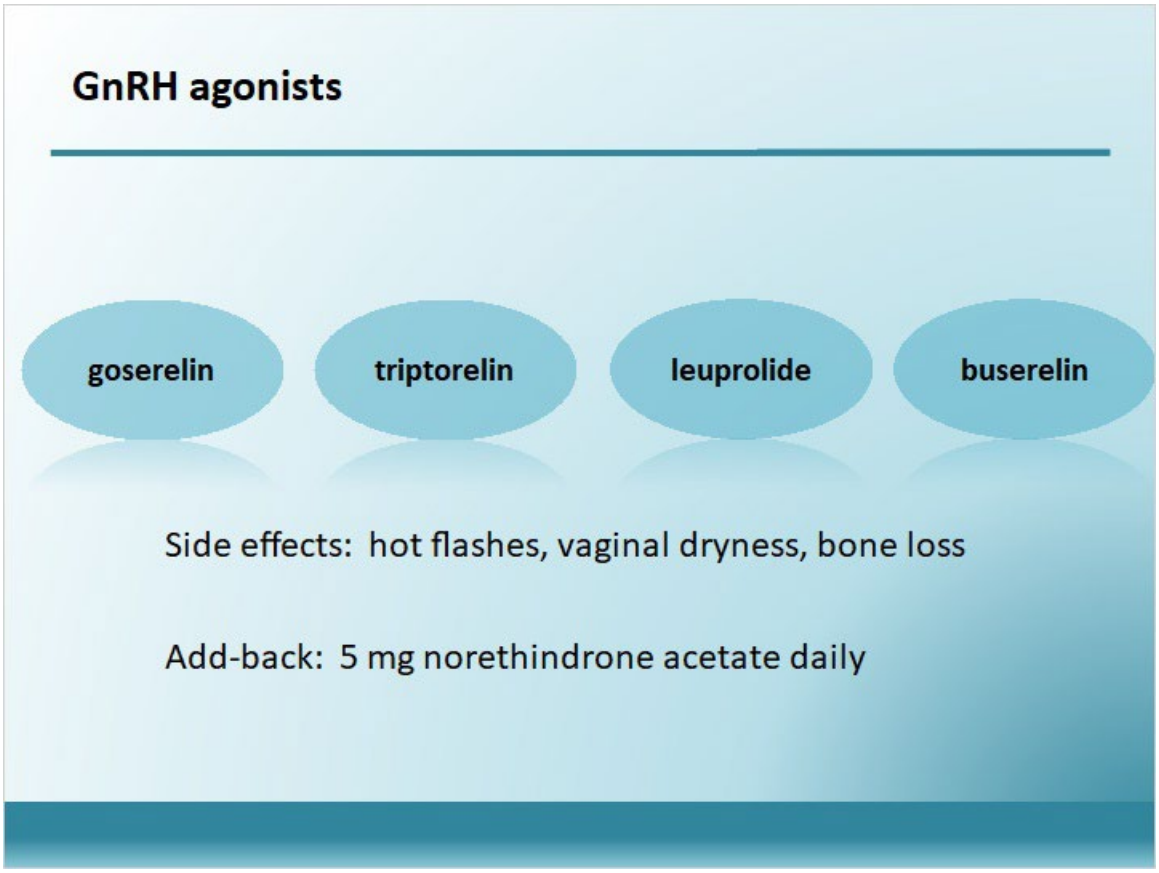
1.7 Untitled Slide



Notes:

GnRH agonists have been hypothesized to preserve ovarian reserve through several mechanisms. Depot GnRH agonist induces downregulation of FSH production, which causes suppression of the pituitary ovarian axis. The lower circulating levels of FSH diminish the accelerated loss of ovarian reserve mediated by FSH-driven follicular recruitment. Another possible mechanism is that GnRH agonists decrease ovarian perfusion. This may decrease delivery of the chemotherapeutic agent to the ovary. Finally, a direct gonadal effect may prevent cellular apoptosis.

1.8 GnRH agonists

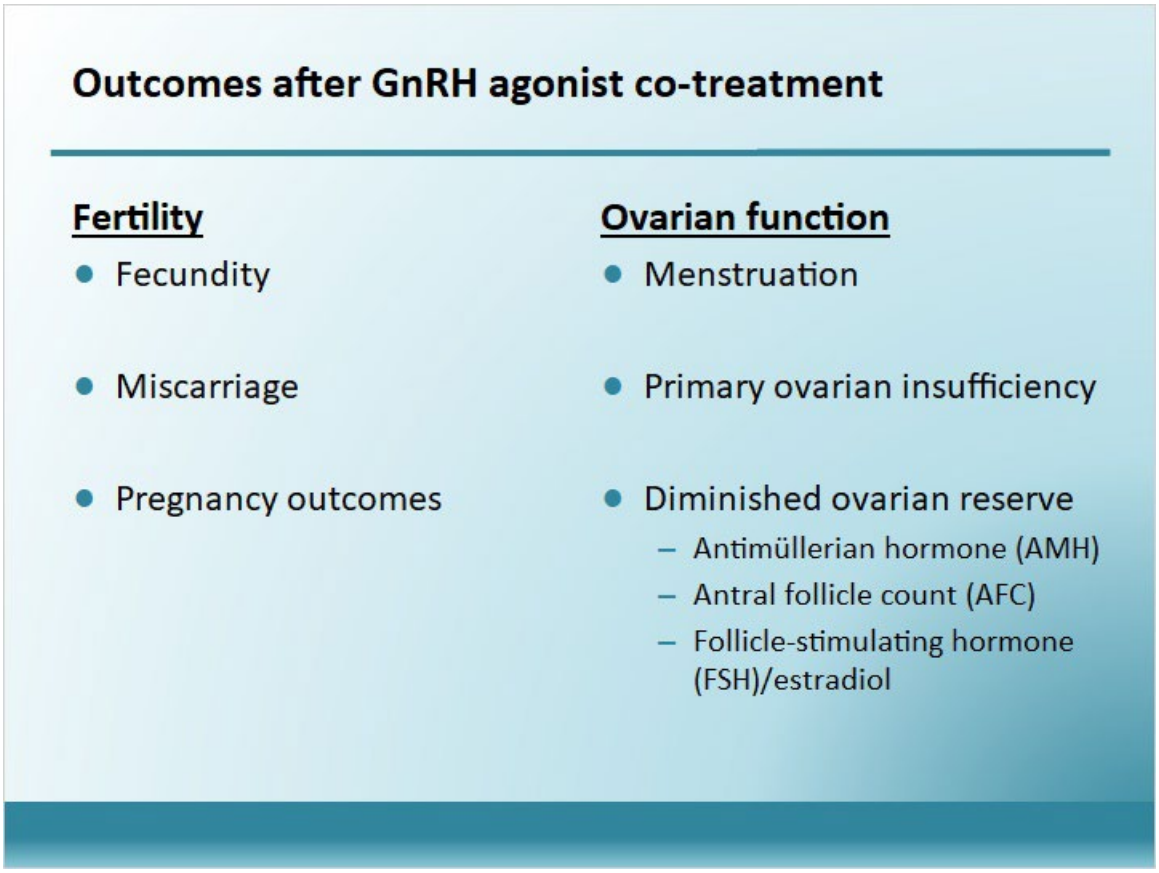


Notes:

Goserelin and triptorelin are the GnRH agonists most often used in recent ovarian protection studies in breast cancer patients, while buserelin and leuprolide have been used in studies published in the 1980s and 1990s as well as in patients with hematologic malignancies. All of these medications have a similar mechanism of action, but their modes of delivery vary. Goserelin is administered through a subcutaneous injection, triptorelin and leuprolide are administered through an intramuscular injection, and buserelin is administered as a nasal spray.

Side effects of GnRH agonists related to the induced hypoestrogenic state include hot flashes, vaginal dryness, and bone loss. If the side effects are bothersome, it is sometimes possible to use medications to 'add back' some reproductive hormones. For example, norethindrone acetate is a progestin with estrogenic properties and has been shown to preserve bone mass and significantly reduce vasomotor symptoms without increasing the rate of vaginal bleeding. Add-back therapy may not be appropriate in women with hormone receptor-positive breast cancer.

1.9 Outcomes after GnRH agonist co-treatment



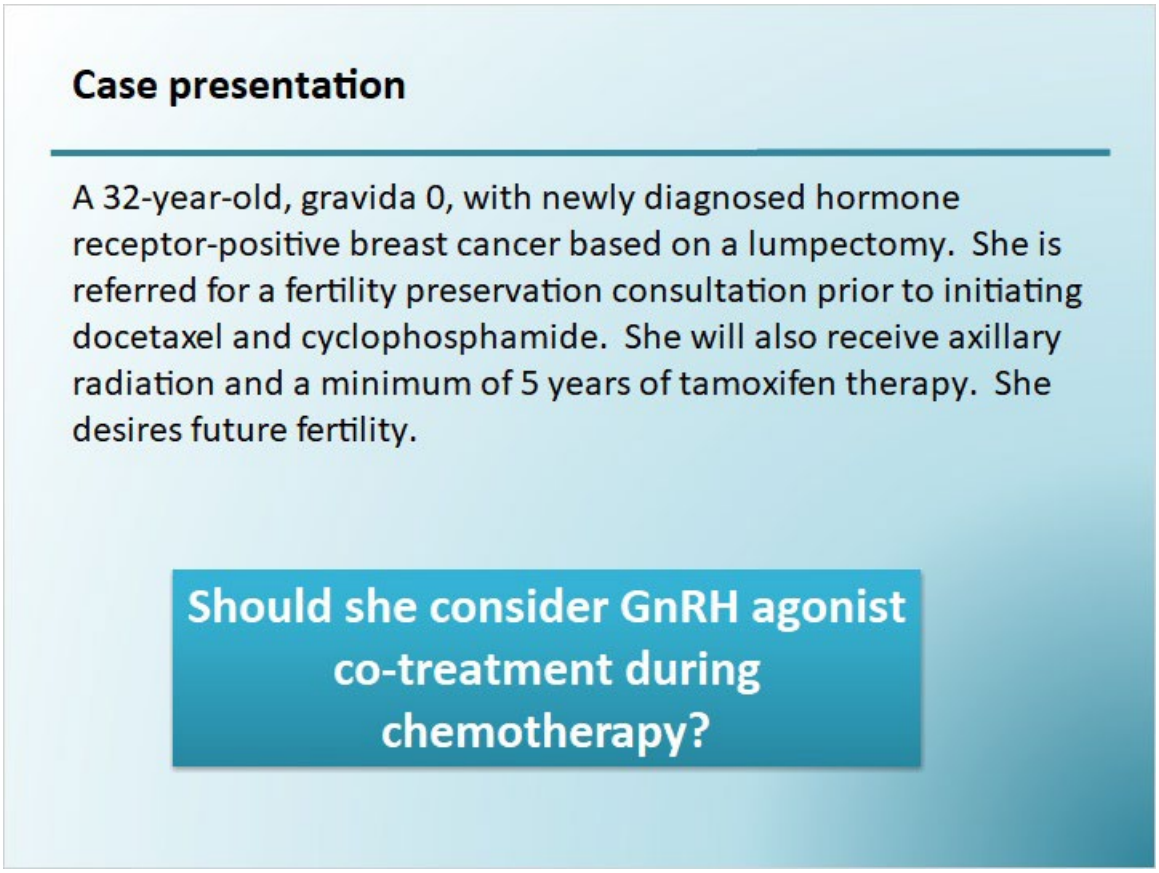
Notes:

Preservation of fertility and ovarian function during cancer treatment are outcomes of interest for many patients and providers.

There are limited randomized data on fertility related outcomes such as fecundity, miscarriage rate, and maternal and neonatal outcomes after co-treatment with a GnRH agonist during chemotherapy. It is difficult and expensive to conduct research that is powered to compare and track long-term outcomes such as fertility.

Most GnRH agonist co-treatment studies are designed to show a difference in the rate of resumption of menses or primary ovarian insufficiency at 1-2 years after chemotherapy.

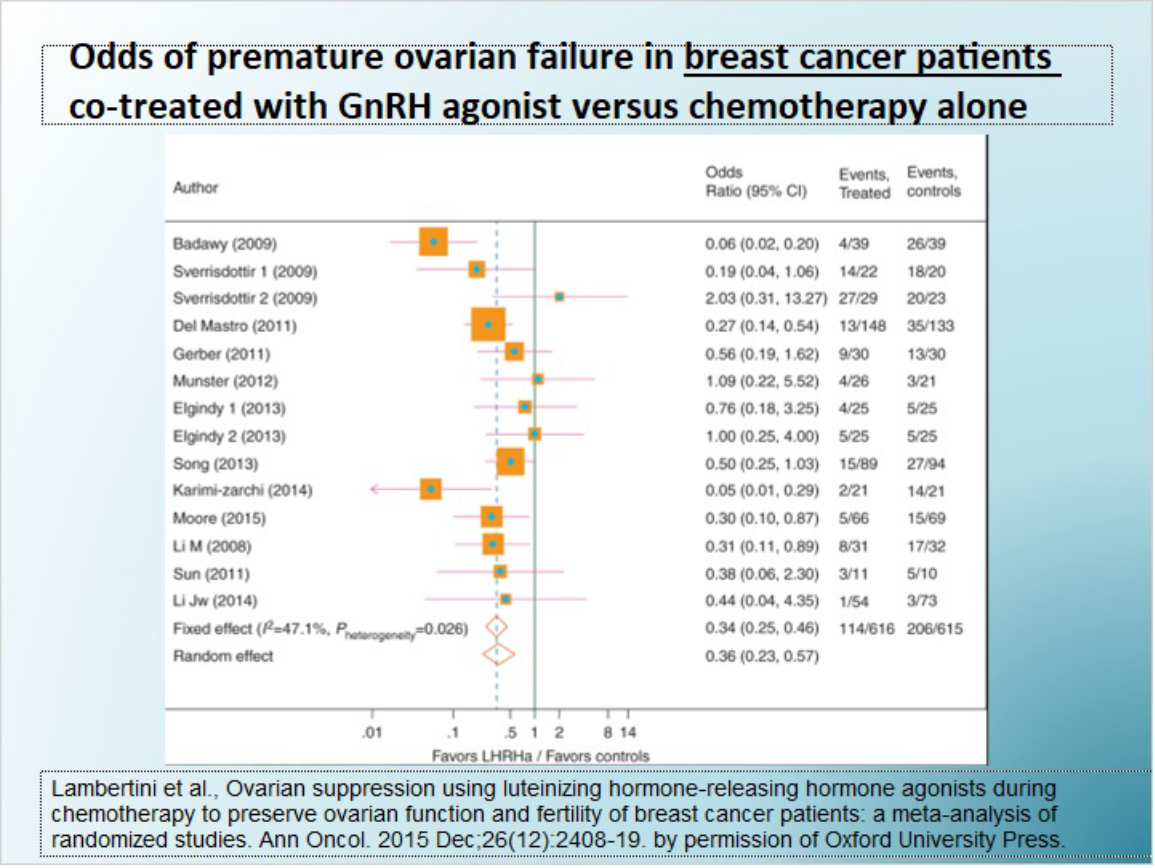
1.10 Case presentation



Notes:

We will analyze the evidence for GnRH agonist co-treatment during chemotherapy in the case of a 32-year-old gravida 0 with newly diagnosed hormone receptor-positive breast cancer based on the pathology obtained from a lumpectomy. She is referred for a fertility preservation consultation prior to initiating docetaxel and cyclophosphamide. She will also receive axillary radiation and a minimum of 5 years of tamoxifen therapy. During the consultation for fertility preservation, the patient is offered ovarian reserve testing and counseled extensively on the option of oocyte banking prior to the start of chemotherapy and she is not interested in ovarian tissue cryopreservation. Should she consider GnRH agonist co-treatment during chemotherapy instead of, or in addition to, oocyte banking prior to chemotherapy?

1.11 Odds of premature ovarian failure in breast cancer patients co-treated with GnRH agonist versus chemotherapy alone

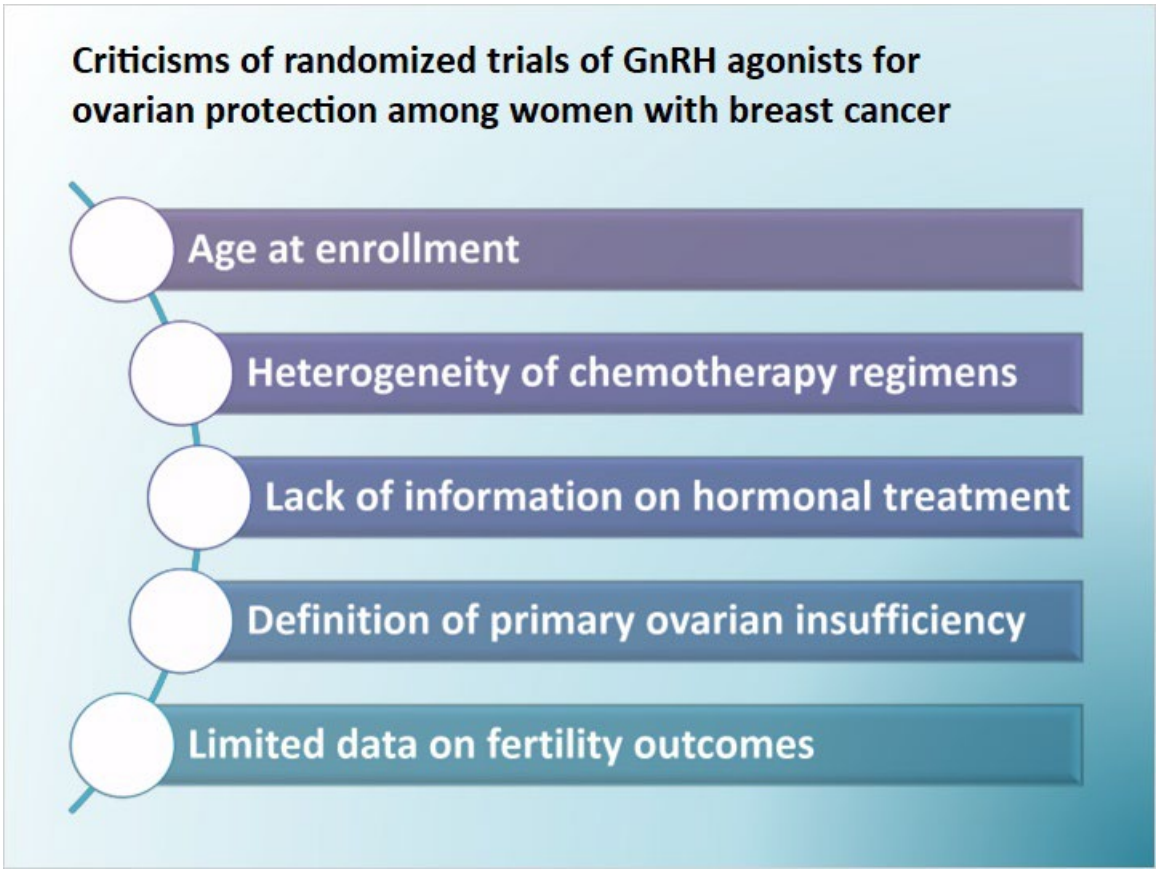


Lambertini et al., Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015 Dec;26(12):2408-19. by permission of Oxford University Press.

Notes:

To date, 12 randomized controlled trials have been published on co-treatment with a GnRH agonist or chemotherapy alone in women with breast cancer. A recent meta-analysis found a significant reduction in the odds of developing premature ovarian failure in women with breast cancer who were co-treated with a GnRH agonist during chemotherapy compared to women who received chemotherapy alone with an odds ratio of 0.34 that favors a GnRH agonist and a 95% confidence interval of 0.025-0.46 and a P value of .026.

1.12 Criticisms of randomized trials of GnRH agonists for ovarian protection among women with breast cancer



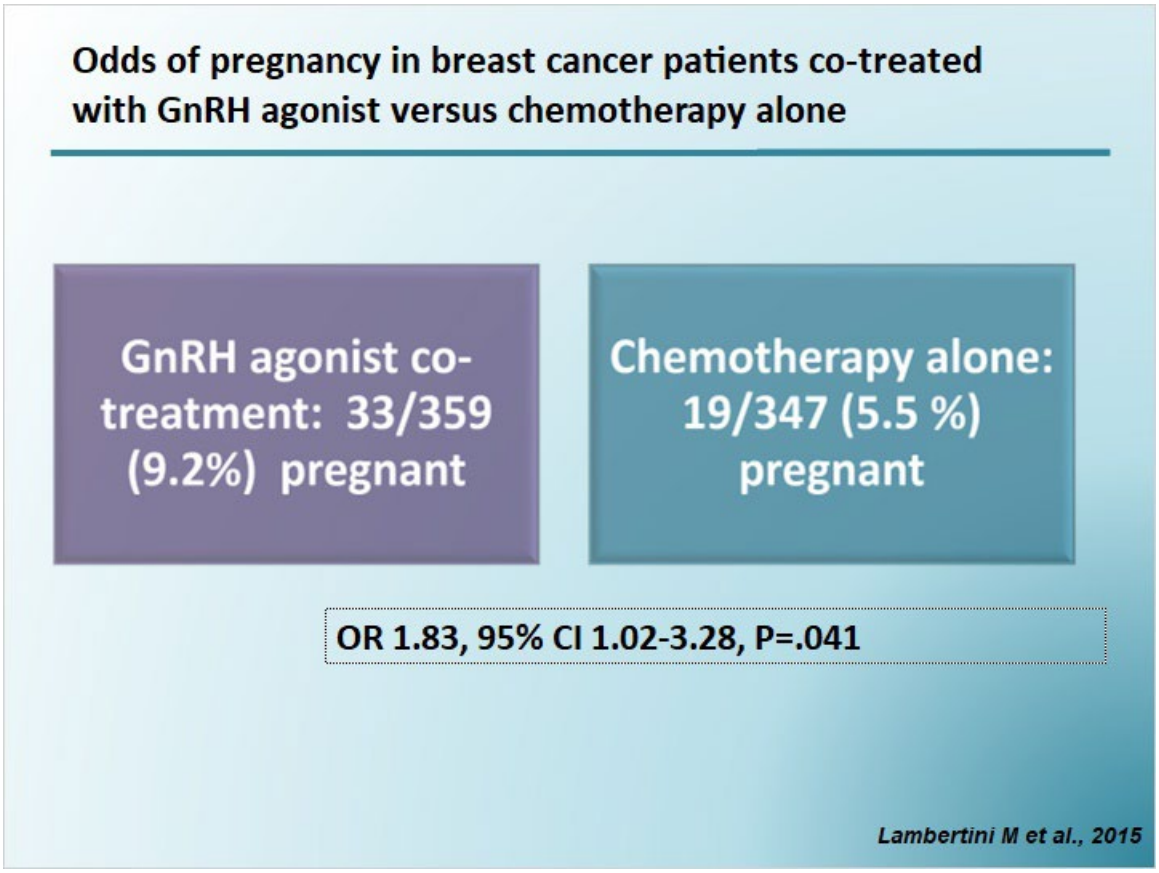
Notes:

Several criticisms of the individual trials and thus the meta-analysis exist:

- Several trials enrolled women in their mid- to late-40s. Given the high rates of infertility and natural menopause in this population, fertility outcomes could not be directly assessed.
- The chemotherapy regimens used in trials performed 20-30 years ago typically included higher cumulative doses of cyclophosphamide and were more ovarian toxic than current regimens that use lower cumulative doses of cyclophosphamide. This resulted in heterogeneity of the chemotherapy regimens in the meta-analysis.
- Several trials include women with hormone-positive cancers that are typically treated with tamoxifen after chemotherapy. Tamoxifen is a confounder as it is associated with amenorrhea. Some studies do not provide information on hormone-positive cancers and treatment with tamoxifen.
- The definition of primary ovarian insufficiency varies among trials. Some studies base the diagnosis solely on patient-reported amenorrhea lasting greater than 6-12 months, whereas others include FSH values in the diagnosis.

- Finally, most studies are powered to show a difference in rate of primary ovarian insufficiency and not fertility outcomes. Of note, several studies were stopped prematurely because of a lack of a benefit noted at the interim analysis. Information on how participants were tracked for fertility outcomes is limited in most of the trials, thus limiting the ability to objectively assess differences in these endpoints.

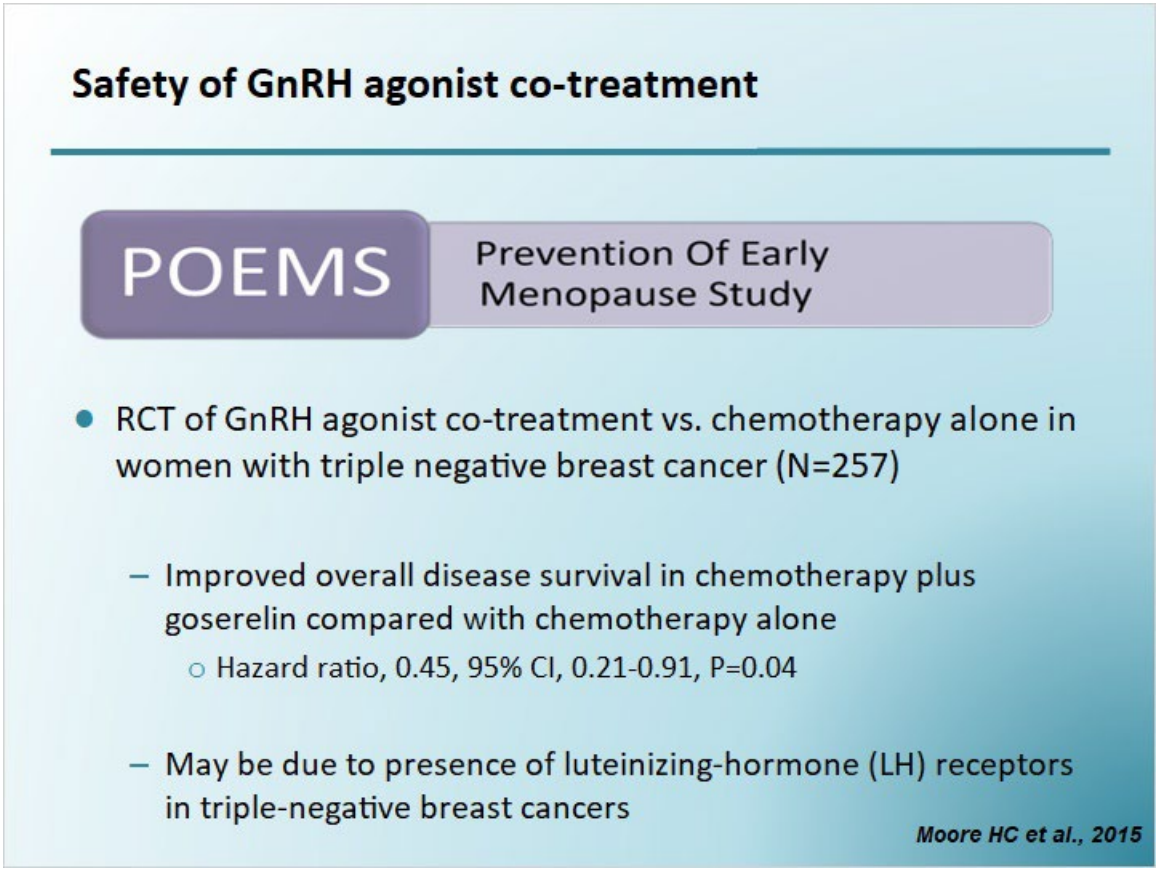
1.13 Odds of pregnancy in breast cancer patients co-treated with GnRH agonist versus chemotherapy alone



Notes:

In the recent meta-analysis that evaluated randomized controlled trials published on co-treatment with a GnRH agonist or chemotherapy alone in women with breast cancer, 5 studies reported the number of patients with pregnancies after breast cancer treatment, although it is unclear if the pregnancies were spontaneous or achieved through fertility treatment. Thirty-three or 9.2% of women who were co-treated with GnRH agonist became pregnant, compared with 19 or 5.5% of women who received chemotherapy alone. GnRH agonist co-treatment was associated with a significantly higher chance of pregnancy.

1.14 Safety of GnRH agonist co-treatment



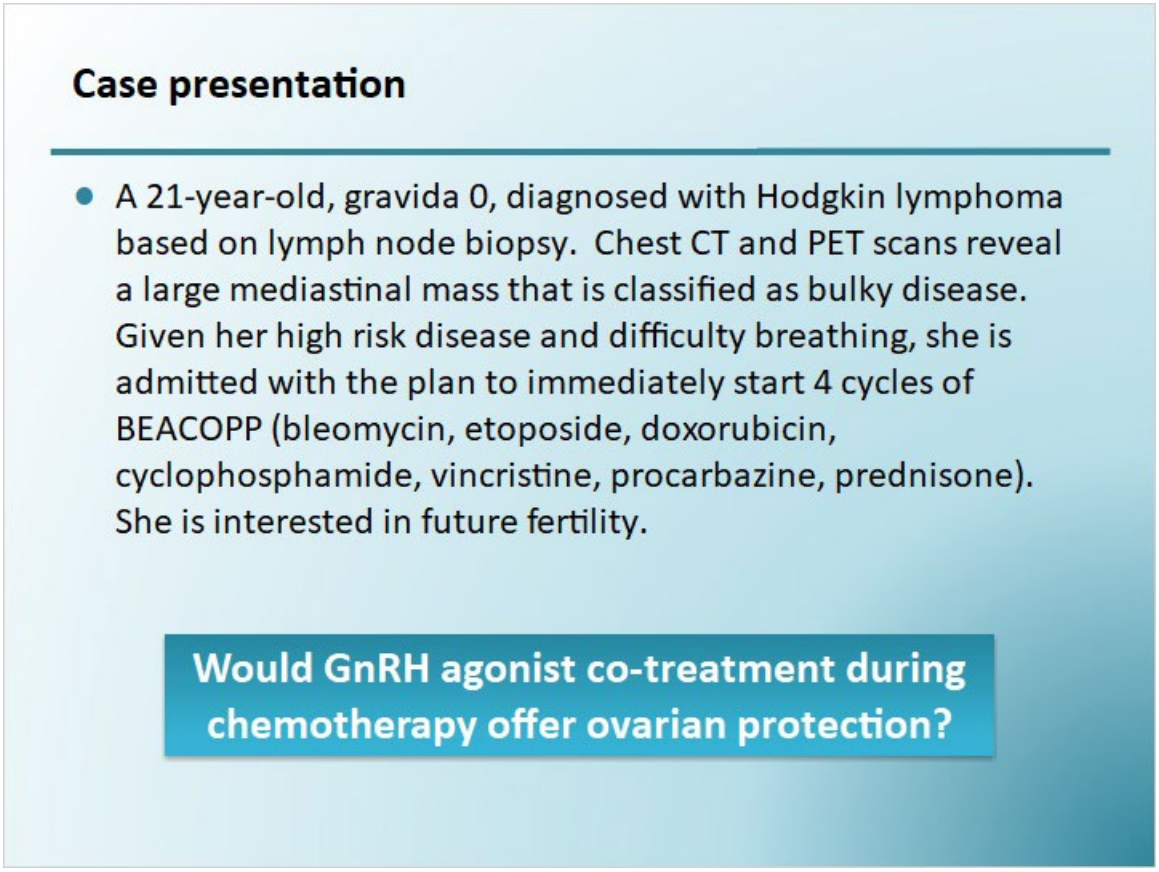
Notes:

In addition to evaluating the efficacy of GnRH agonist co-treatment, multiple studies have evaluated the safety of this approach with respect to disease-free and overall survival in women with breast cancer.

In the Prevention Of Early Menopause Study (POEMS), women with hormone-receptor-negative early-stage breast cancer were randomized to co-treatment with goserelin versus chemotherapy alone. Women with hormone receptor-negative early breast cancer were studied to eliminate the confounder of tamoxifen induced amenorrhea. Despite closing the trial early due to funding issues, a reduction in primary ovarian failure was observed with goserelin co-treatment. In addition, a nonsignificant trend toward disease-free survival, as well as a significant increase in overall survival, was observed in the goserelin group, suggesting safety of GnRH agonist co-treatment in women with triple-negative cancer. A possible explanation for this finding is that luteinizing hormone (LH) receptors are frequently present in triple-negative cancers. Preclinical studies have shown that the use of GnRH analogs in xenograft models of

triple-negative breast cancer is associated with growth inhibition, reduction in metastasis, and apoptotic cell death in xenograft models of triple-negative breast cancer. It is possible that the GnRH agonist co-treatment may contribute to obtaining remission and it does not appear that ovarian protection is harmful for disease-free women or to overall survival among women with triple-negative breast cancer.

1.15 Case presentation

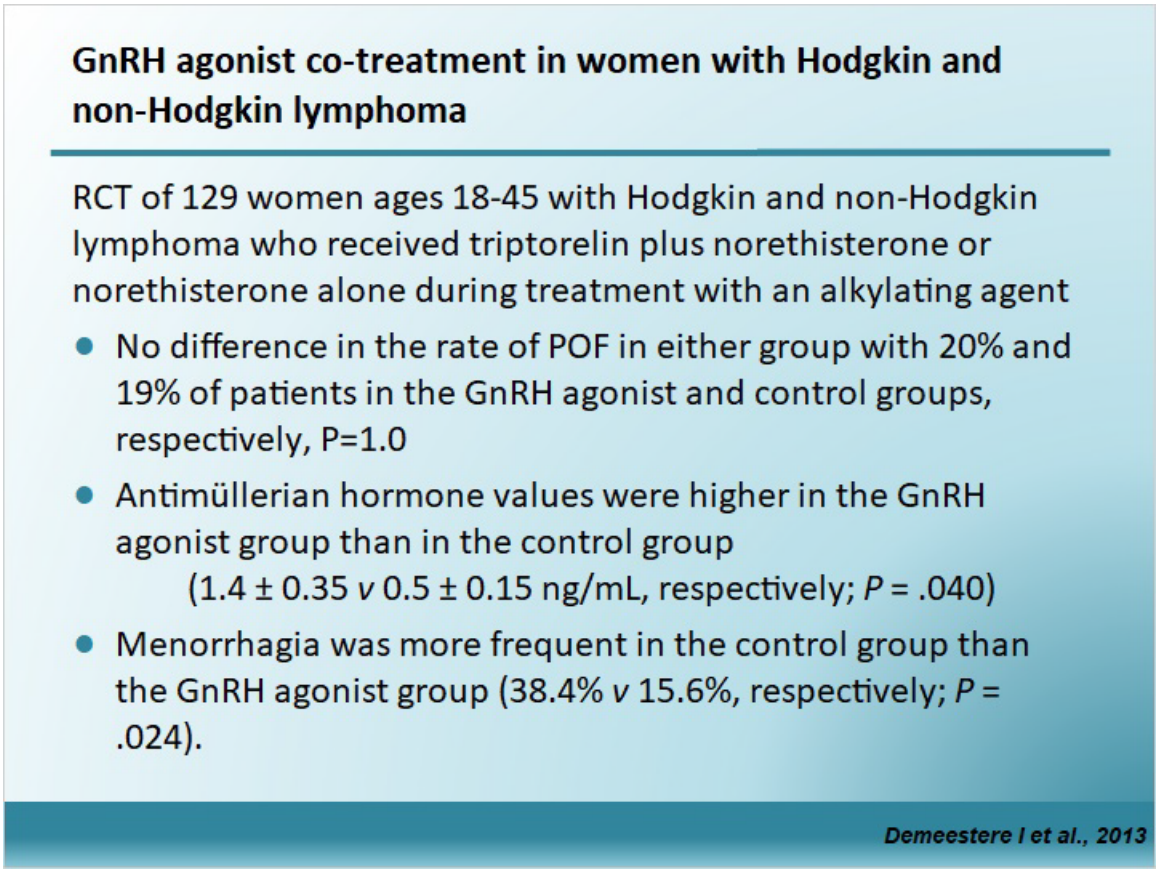


Notes:

Next we will evaluate the role of GnRH agonist co-treatment in a 21-year-old gravida 0 woman with Hodgkin lymphoma based on lymph node biopsy. Chest CT and PET scans reveal a large mediastinal mass that is classified as bulky disease. Given her high-risk disease and difficulty breathing, she is admitted with the plan to immediately start 4 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). During the consultation for fertility preservation, the patient is offered ovarian reserve testing. She is counseled that she is not a candidate for oocyte or ovarian tissue banking due to the immediate need to start chemotherapy and her state of health. Would GnRH agonist co-treatment during chemotherapy offer ovarian

protection?

1.16 GnRH agonist co-treatment in women with Hodgkin and non-Hodgkin lymphoma

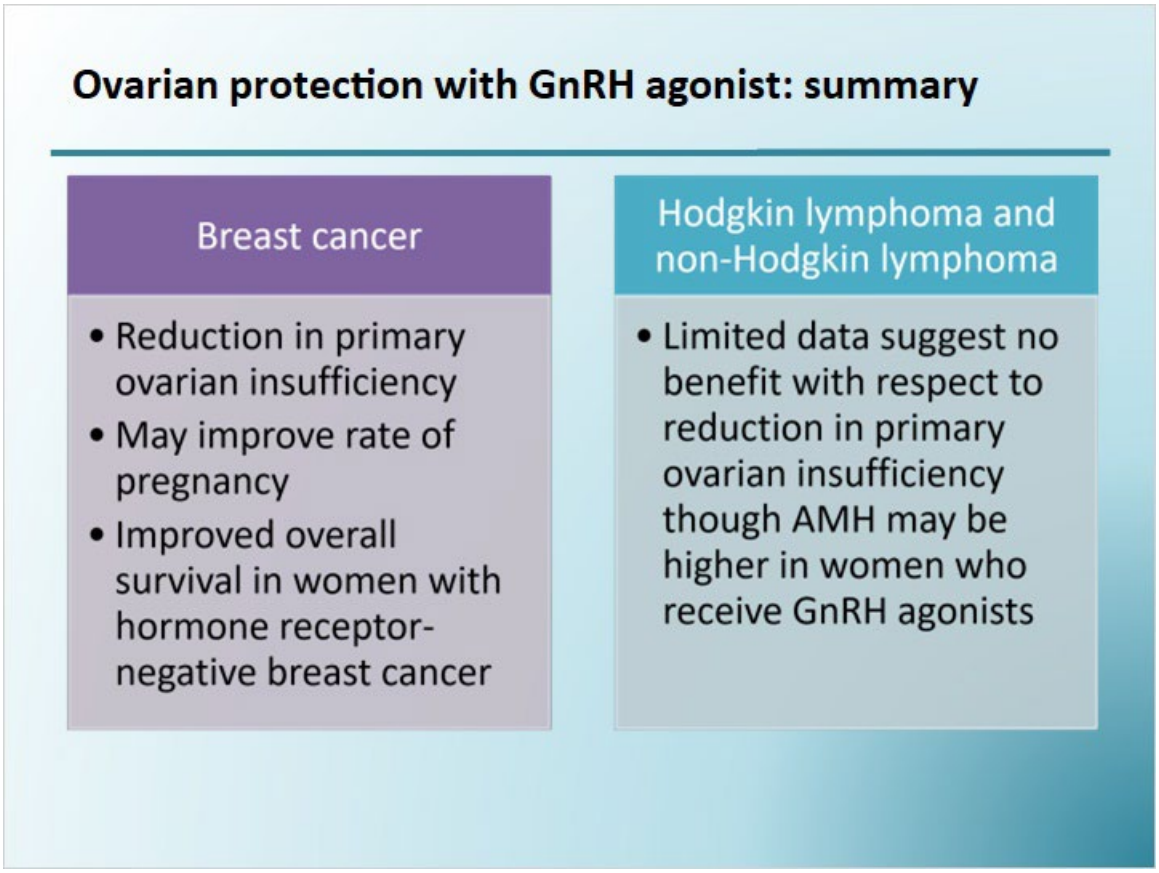


Notes:

The largest randomized trial in women with Hodgkin and non-Hodgkin lymphoma included 129 women ages 18-45 who received triptorelin plus norethindrone or norethindrone alone during treatment with an alkylating agent. The primary endpoint was premature ovarian failure at one year of follow up. After 1 year, 20% and 19% of patients in the GnRH agonist and control groups, respectively, exhibited premature ovarian failure (*P* = 1.00). More than half of patients in each group completely restored their ovarian function (FSH <10 IU/L), but the antimüllerian hormone values were higher in the GnRHa group than in the control group (1.4 ± 0.35 *v* 0.5 ± 0.15 ng/mL, respectively; *P* = .040). The occurrence of adverse events was similar in both groups with the exception of metrorrhagia, which was more frequently observed in the control

group than the GnRHa group (38.4% *v* 15.6%, respectively; *P* = .024).

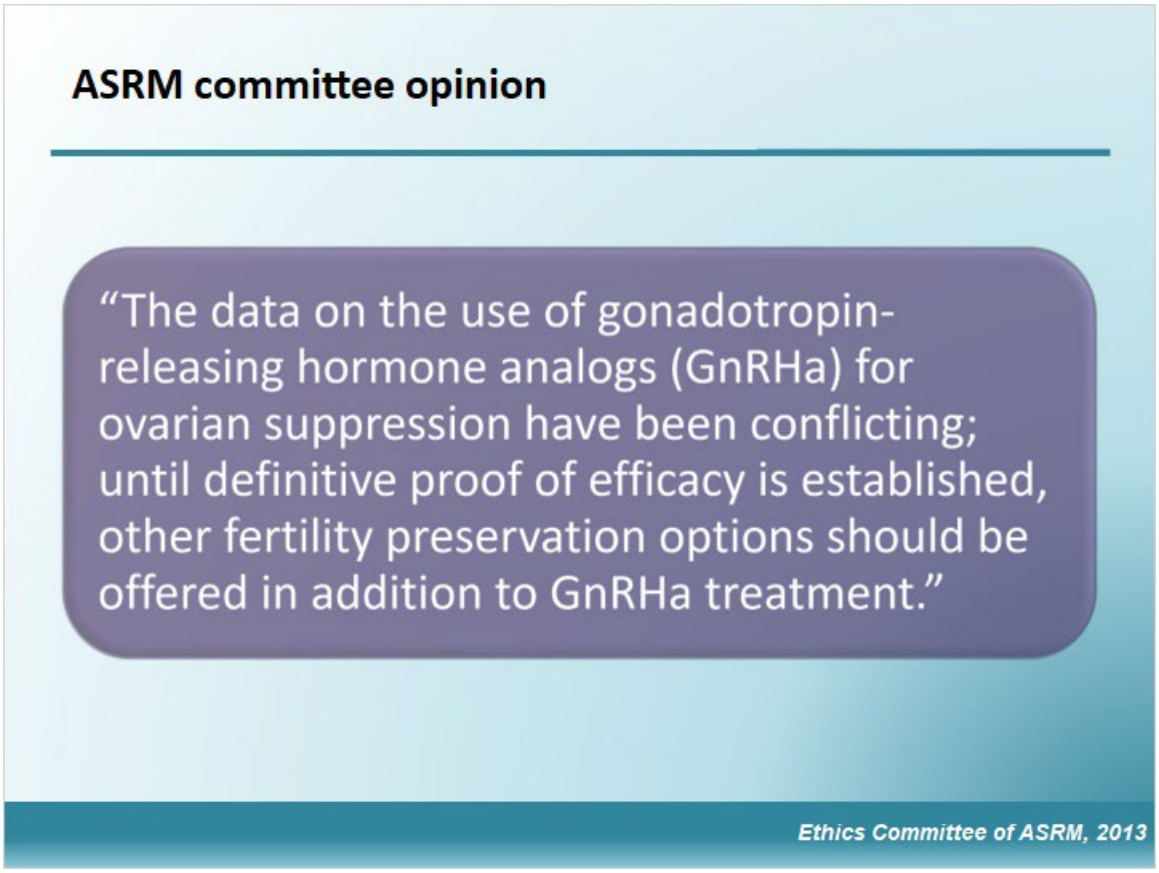
1.17 Ovarian protection with GnRH agonist: summary



Notes:

In summary, meta-analysis data support the use of GnRH agonist co-treatment during chemotherapy for breast cancer in order to reduce the number of women who experience primary ovarian insufficiency. This approach may also improve the rate of pregnancy among breast cancer survivors and appears to be safe in certain types of breast cancer. There are limited data in women with Hodgkin and non-Hodgkin lymphoma. The current data do not suggest that this approach is effective at reducing the number of women who experience primary ovarian insufficiency after treatment with an alkylating agent, though it may be associated with higher AMH levels 1 year post treatment. There are no data on GnRH agonist co-treatment for women receiving treatment for sarcomas, gastrointestinal, or gynecologic malignancies.

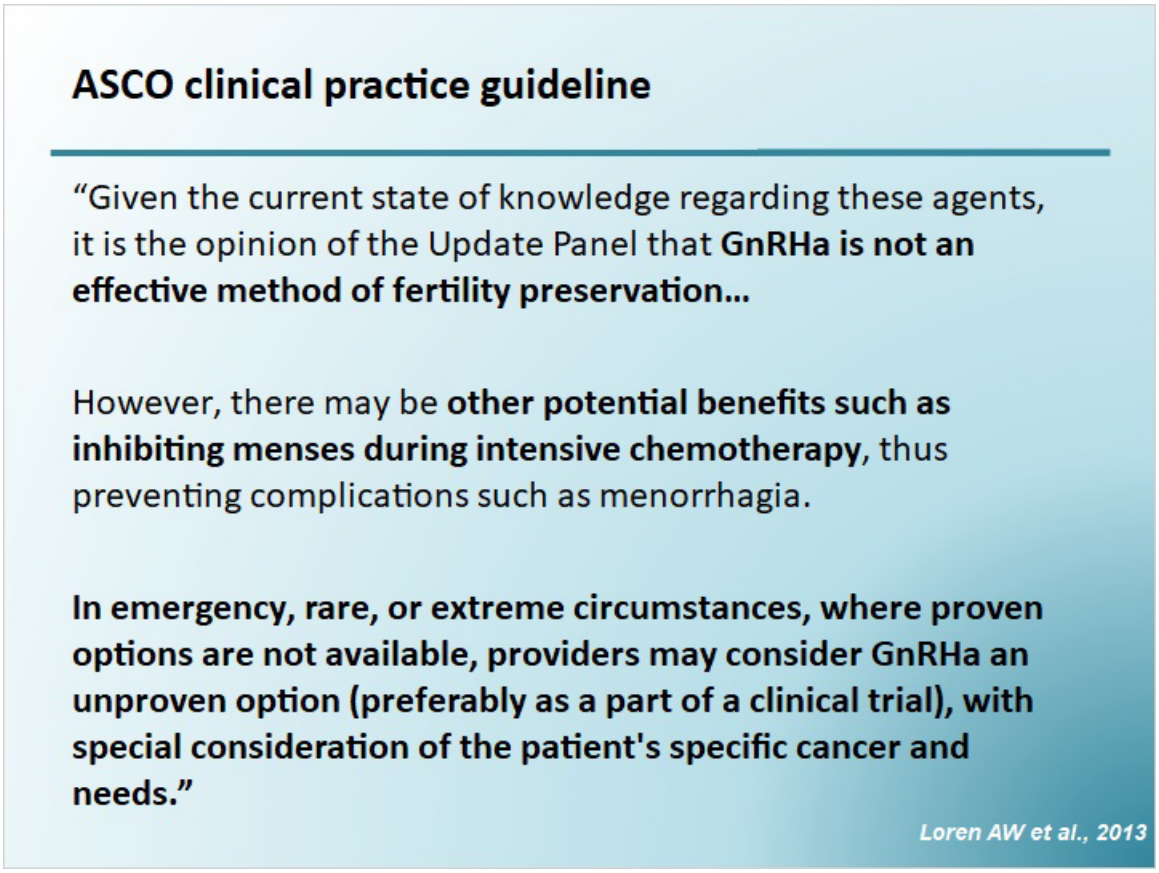
1.18 ASRM committee opinion



Notes:

A 2013 ASRM committee opinion states that the data on the use of gonadotropin-releasing hormone analogs for ovarian suppression have been conflicting, and that until definitive proof of efficacy is established, other fertility preservation options should be offered in addition to GnRH analog treatment.

1.19 ASCO clinical practice guideline

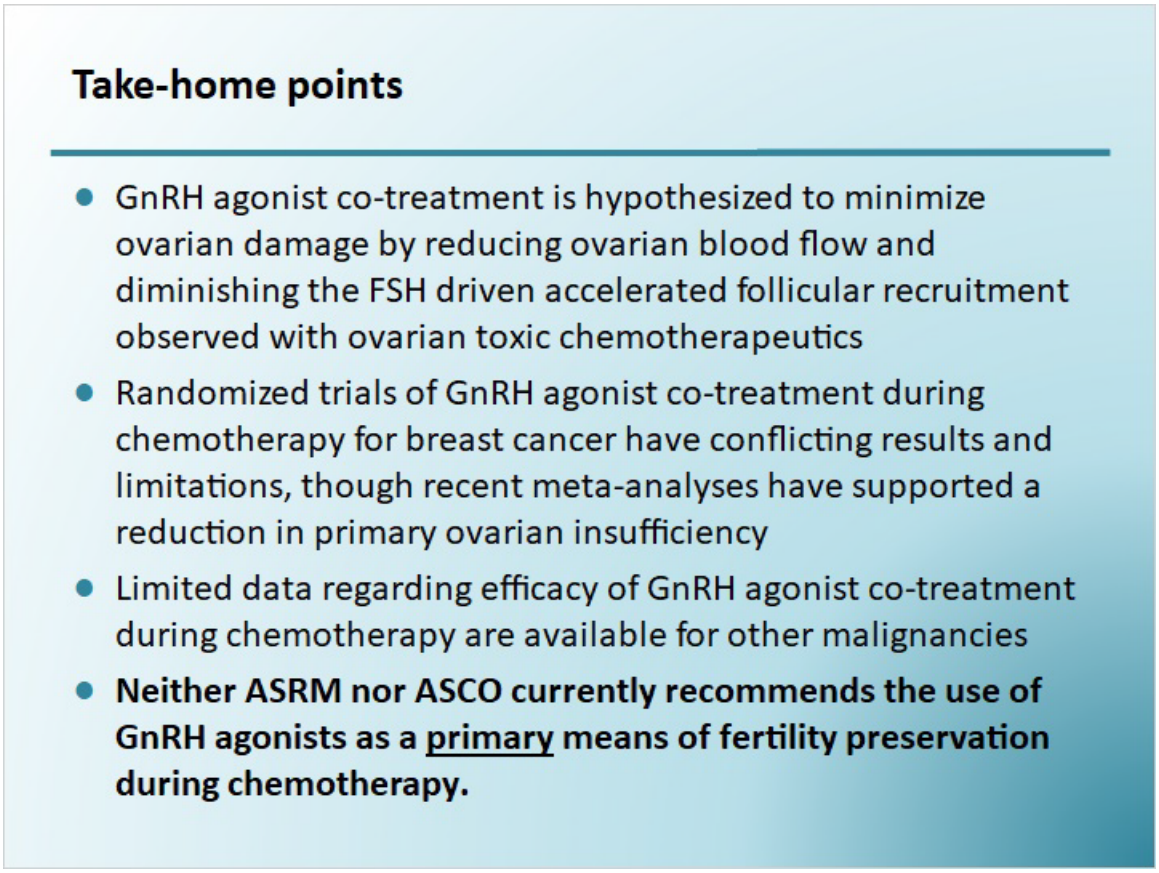


Notes:

Similarly, ASCO released the following statement on the use of GnRH agonist co-treatment during chemotherapy as a method of fertility preservation. It is recommended that GnRH agonist co-treatment be offered as a means of fertility preservation in addition to, but not instead of, IVF with cryopreservation of embryos, ova, or ovarian tissue.

Neither the ASRM nor ASCO recommendations has been updated to reflect a change in opinion after the recent publications supporting a benefit for GnRH agonist co-treatment in women with breast cancer.

1.20 Take-home points



Notes:

In summary, GnRH agonist co-treatment is hypothesized to diminish the FSH-driven accelerated follicular recruitment observed with ovarian toxic chemotherapeutics and may diminish blood flow to the ovaries. Randomized trials of GnRH agonist co-treatment during chemotherapy for breast cancer have conflicting results and limitations, though recent meta-analyses have supported a reduction in rates of primary ovarian insufficiency with GnRH agonist use. At the current time, neither ASRM nor ASCO recommends GnRH agonists as a primary means of fertility preservation during chemotherapy, though ASRM acknowledges that GnRH agonists may be offered as an adjunct to other fertility preservation options.

1.21 Thank you!

Notes:

Thank you for your participation. We hope you enjoyed this presentation.