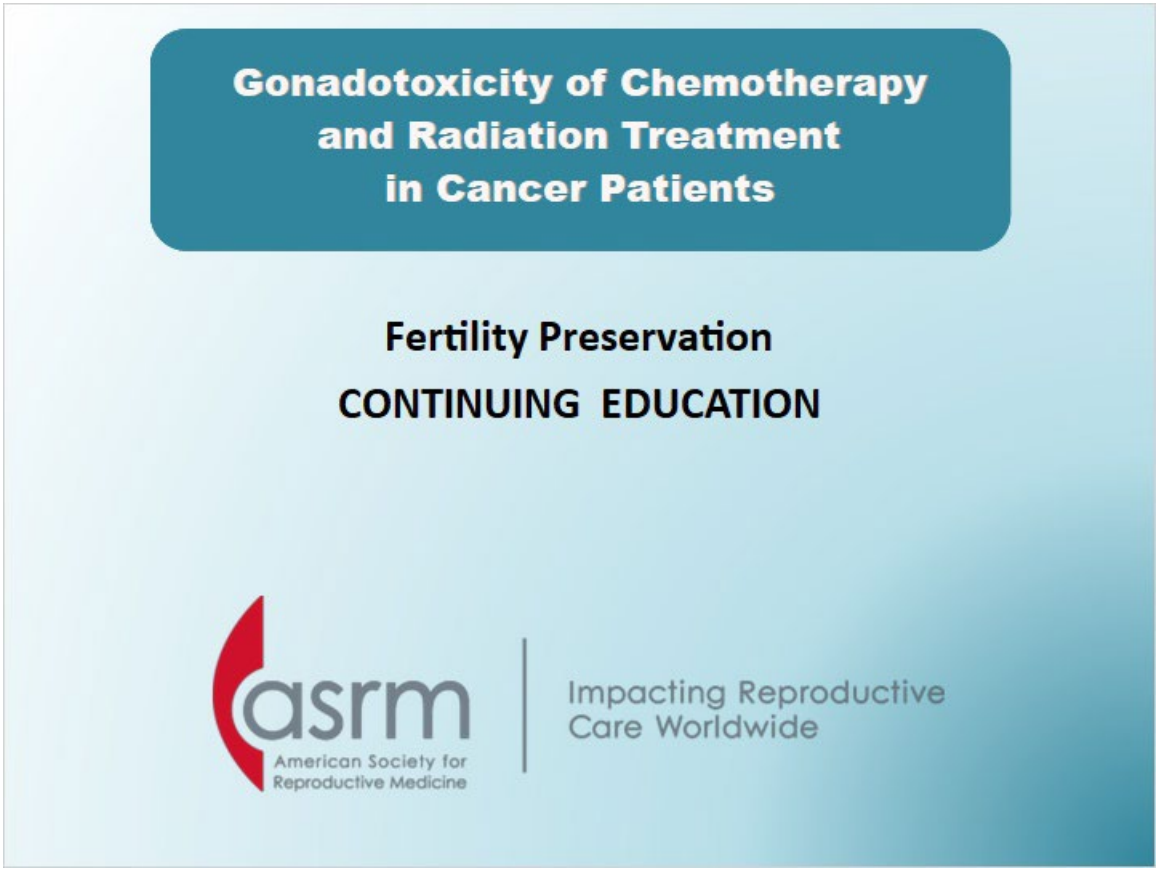
MD120 Lesson 2

1. MD120_L2

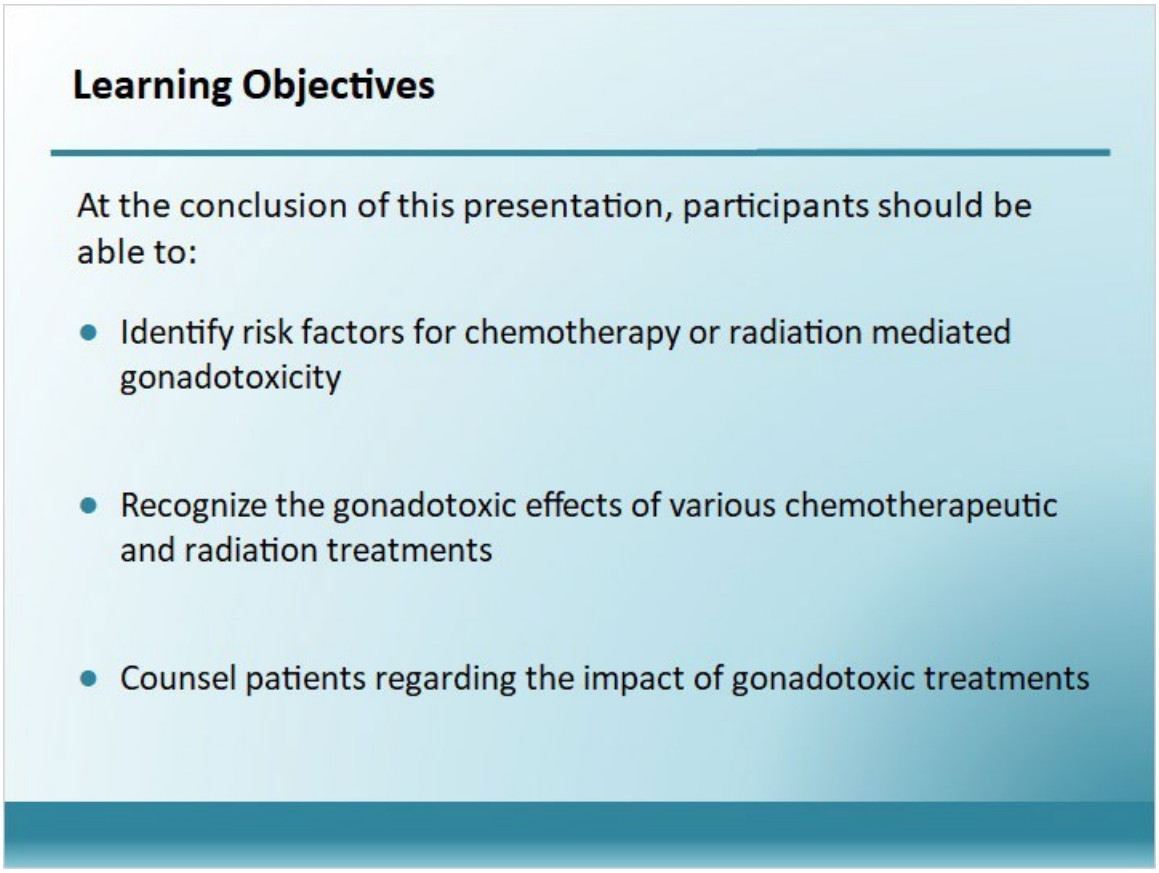
1.1 Gonadotoxicity of Chemotherapy and Radiation Treatment



Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Gonadotoxicity of Chemotherapy and Radiation Therapy in Cancer Patients."

1.2 Learning Objectives

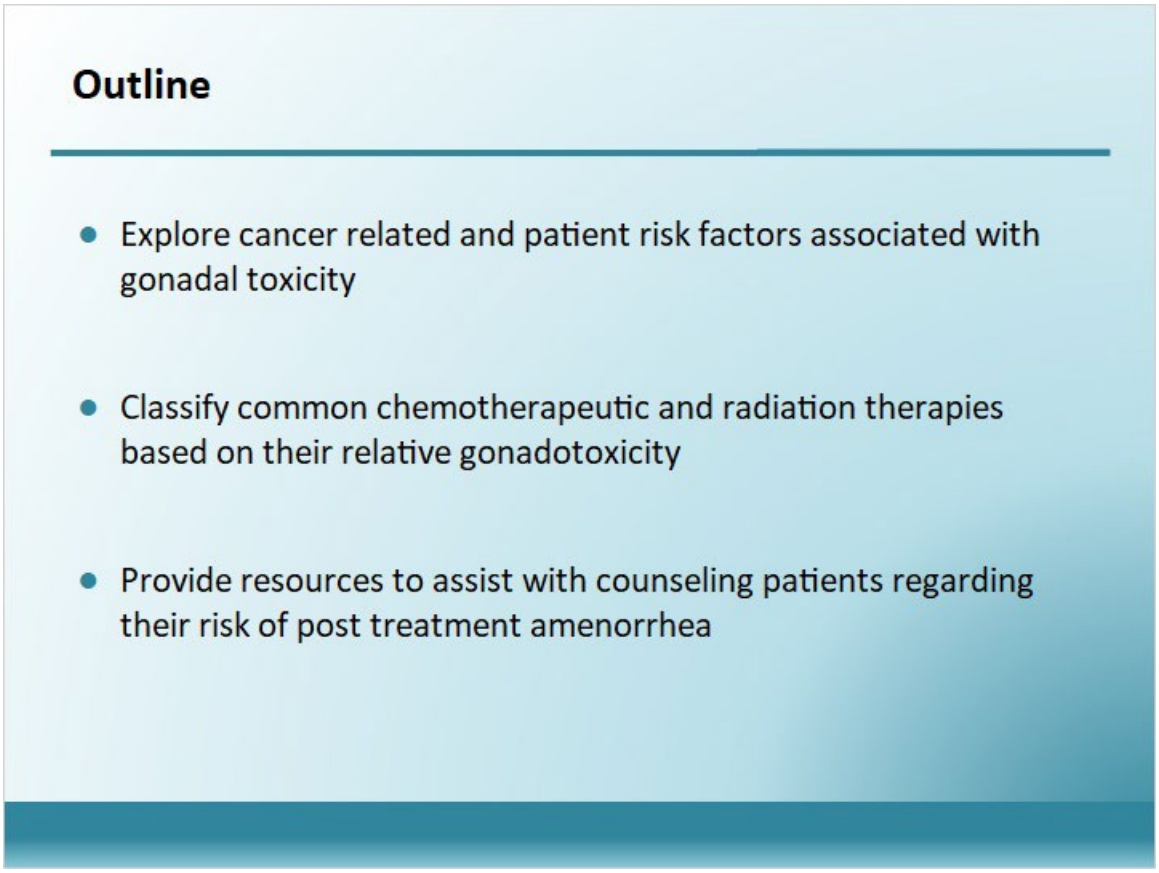


Notes:

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

Identify key risk factors for chemotherapy or radiation mediated gonadotoxicity
Recognize the gonadotoxic effects of various chemotherapeutic and radiation treatments
Counsel patients regarding the impact of gonadotoxic treatments

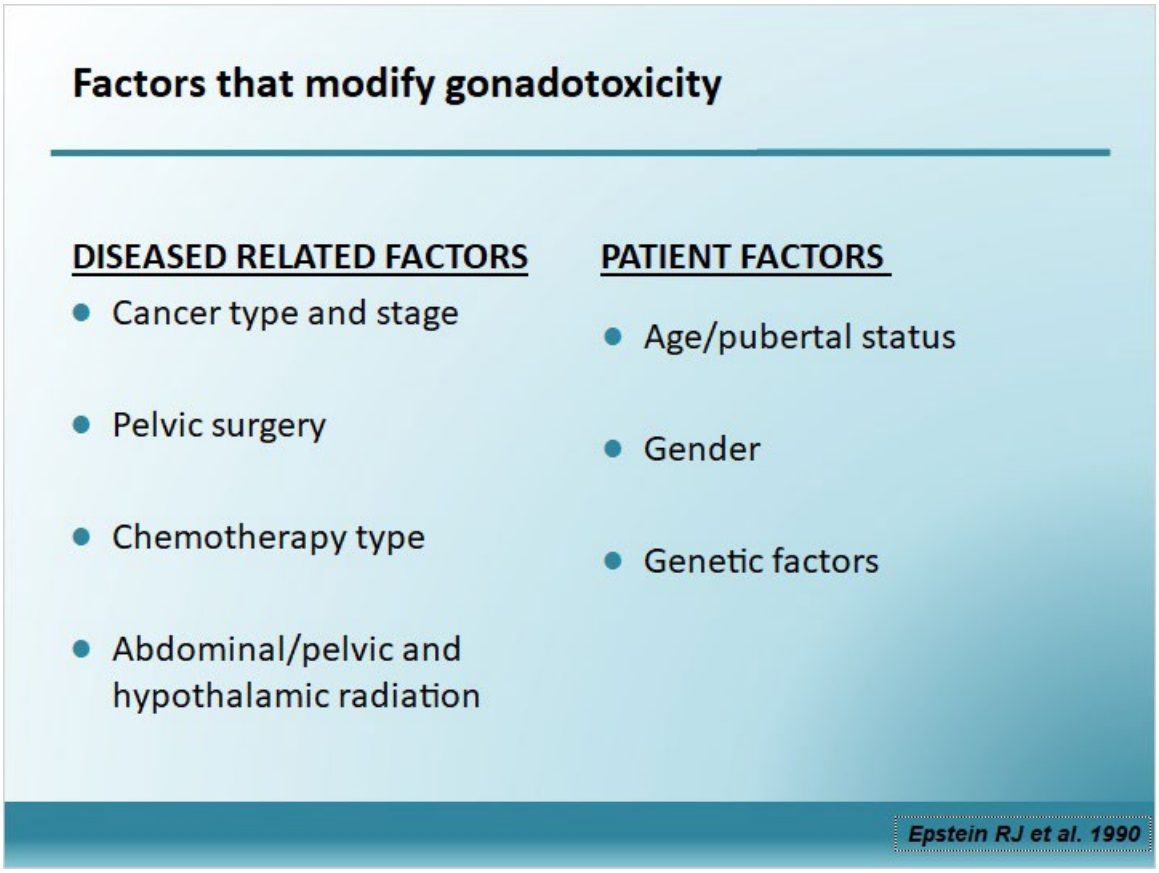
1.3 Outline



Notes:

This presentation will begin by briefly exploring cancer related and patient risk factors associated with gonadotoxicity. The presentation will then classify common chemotherapeutic and radiation therapies based on their relative gonadotoxicity. Finally, the presentation will conclude by reviewing existing resources to assist with counseling patients regarding their risk of post treatment amenorrhea. Note that several related topics are covered in detail in other modules in this course, including: Fertility Preservation Counseling Prior to Treatment for Common Cancers and Benign Conditions, use of Gonadotropin-releasing Hormone (GnRH) Agonists for Fertility Preservation. Additionally, assessment of ovarian function after cancer therapy is covered in the Overview of the Initial Fertility Preservation Consultation and Survivorship modules.

1.4 Factors that modify gonadotoxicity

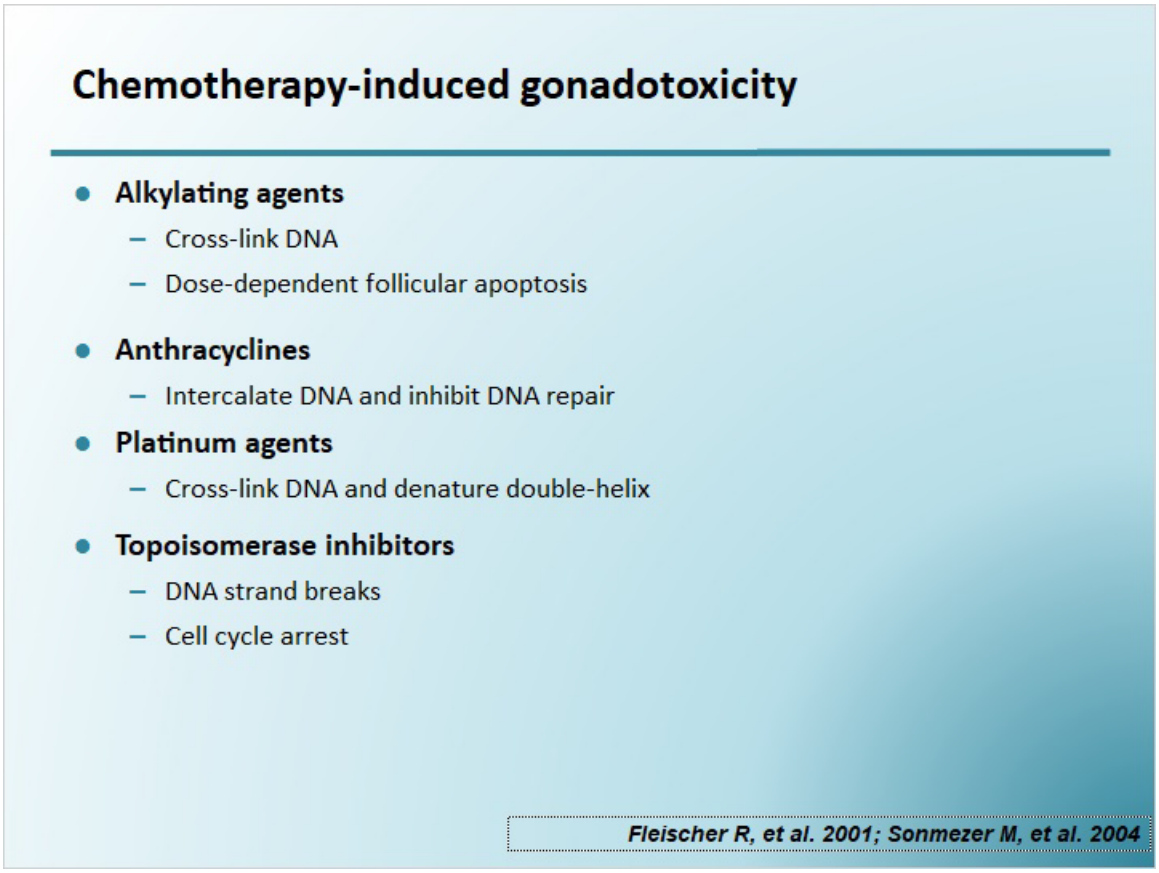


Notes:

Gonadal toxicity is dependent on factors related to the disease, proposed treatment and patient characteristics. Gynecologic malignancies may require surgical management that can adversely impact fertility, though fertility sparing treatment options have been developed for select candidates. Fertility sparing treatment for gynecologic malignancies is covered in detail in a separate module. Alkylating agents induce DNA damage and can reduce ovarian reserve when given in low doses for short durations. Higher doses of alkylating agents in combination with total body irradiation often lead to premature ovarian insufficiency.

Patient characteristics such as age, gender, and genetic factors further modify the risk of gonadotoxicity. As ovarian reserve declines with age, lower doses of alkylating agents and radiation can precipitate premature ovarian insufficiency or menopause. Gender is also a factor as pre-pubertal boys are more susceptible to gonadotoxicity from chemotherapy and radiation than are girls at the same age. Genetic factors, such as BRCA mutations, may also be associated with reduced ovarian reserve.

1.5 Chemotherapy-induced gonadotoxicity



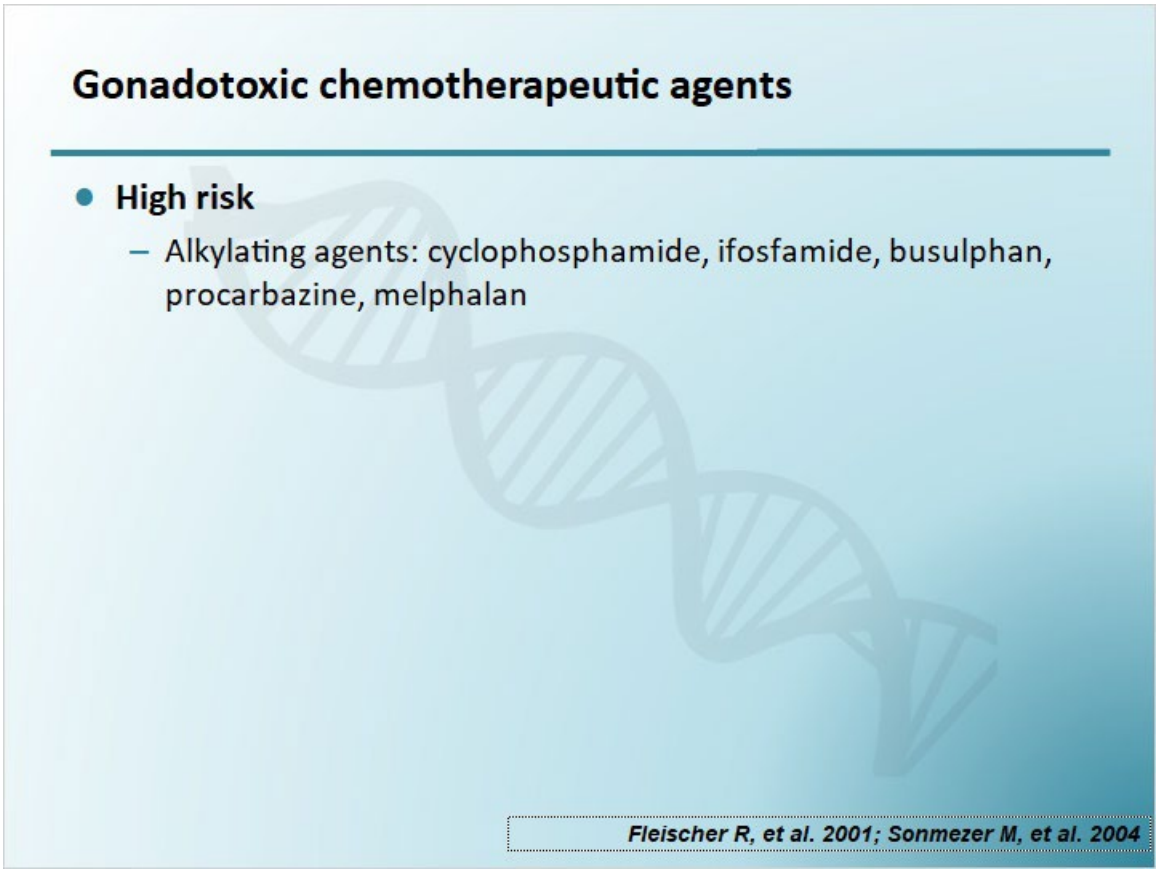
Notes:

Chemotherapeutic agents exert an anti-neoplastic effect by inducing DNA damage in order to arrest cell proliferation. Several of these agents can also have a detrimental impact on gonadal tissue. We will highlight the primary mechanism of action of a few significant agents.

Alkylating agents are among the most gonadotoxic. These agents act by preventing cell division by cross-linking DNA strands and decreasing DNA synthesis. Histologic studies have demonstrated dose-dependent, direct destruction of ova as well as follicular depletion after exposure to alkylating agents.

Anthracyclines, platinum agents, and topoisomerase inhibitors are variably gonadotoxic. Anthracyclines are thought to limit DNA replication and transcription by direct binding to DNA (intercalation) and inhibiting DNA repair (topoisomerase II inhibition). Platinum agents inhibit DNA synthesis by the formation of DNA cross-links resulting in denaturation of the double helix formation. In addition to causing DNA strand breaks, topoisomerase inhibits may delay transit of cells through the S phase resulting in cell cycle arrest.

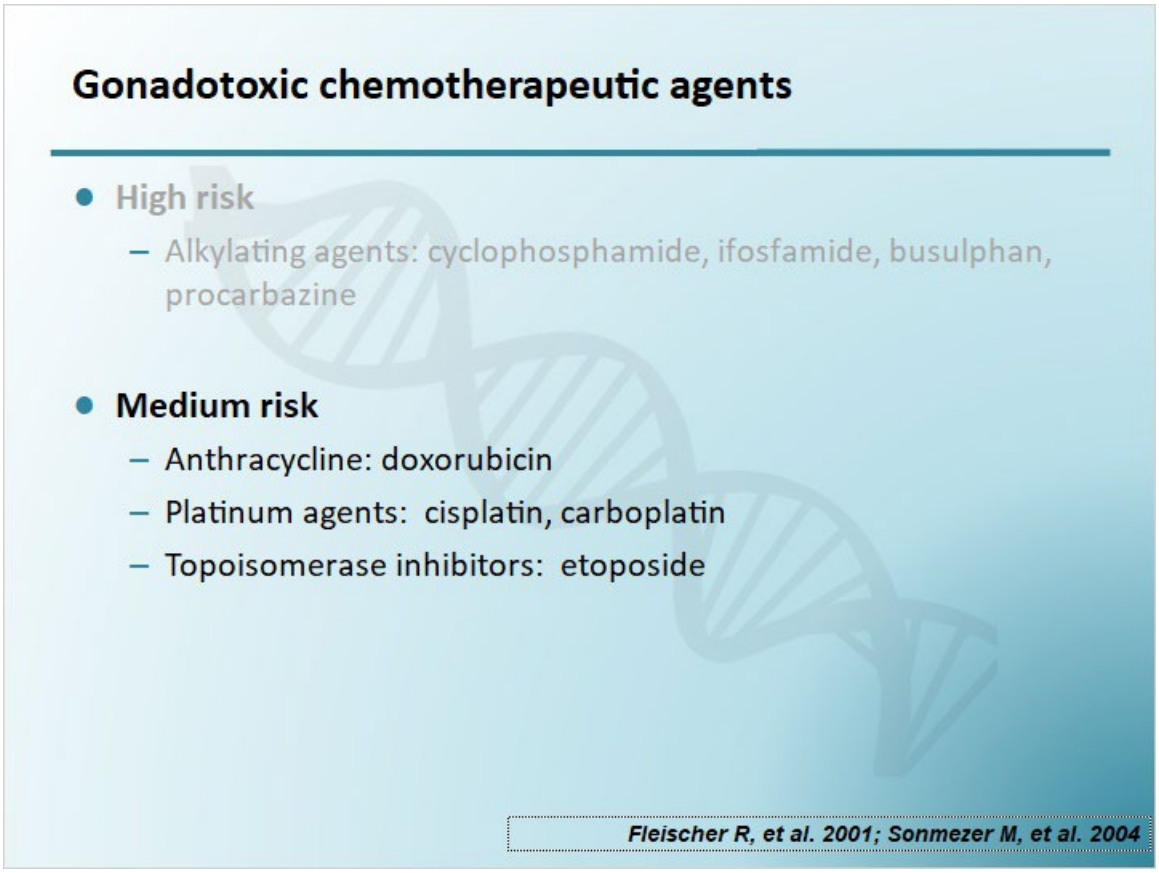
1.6 Gonadotoxic chemotherapeutic agents



Notes:

The extent to which specific chemotherapeutic agents impact developing follicles varies based on the agent. While it is difficult to quantify the risk associated with exposure to a specific agent, it can be helpful for patient counseling to broadly classify chemotherapeutic agents as posing a high, medium, or low risk to gonadal function. As discussed on the previous slide, alkylating agents carry among the highest risks of gonadotoxicity. Cyclophosphamide is one of the most common alkylating agents and is frequently used in the treatment of breast cancer, sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and chronic lymphocytic leukemia.

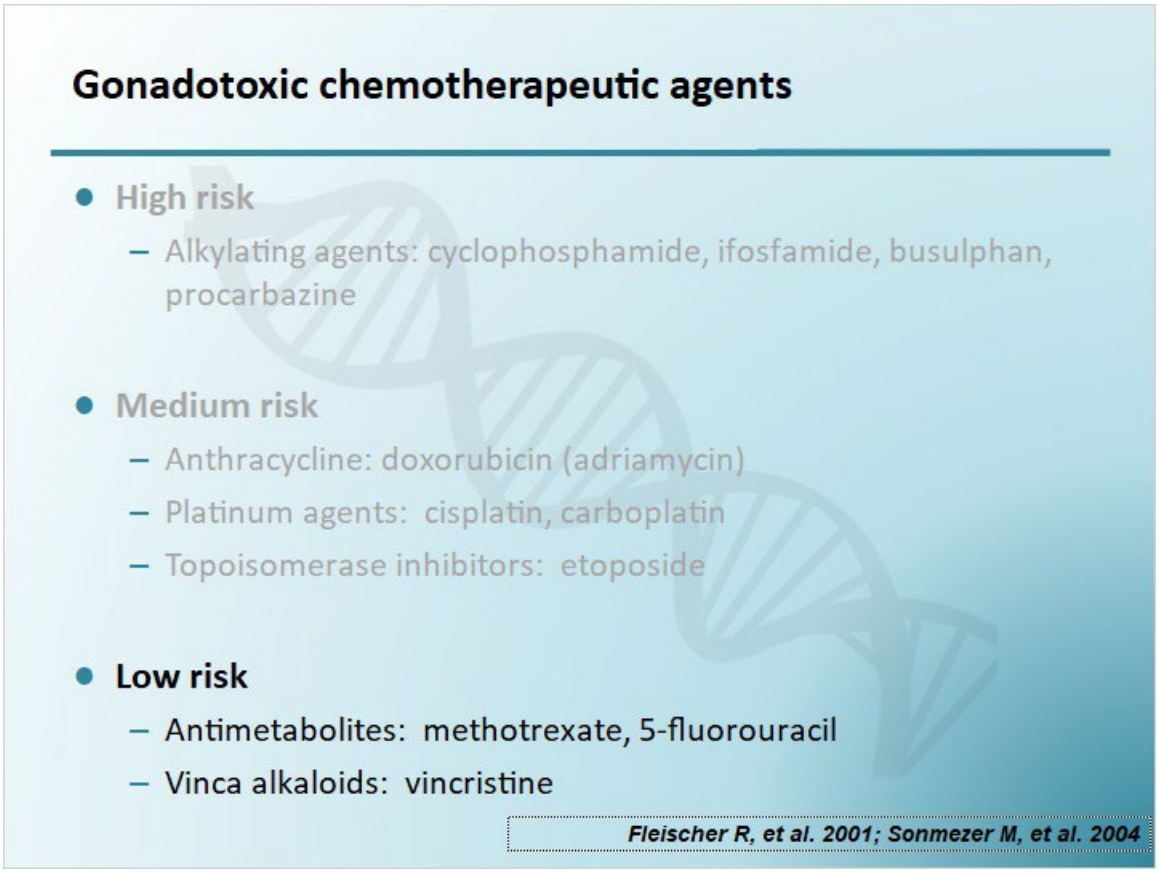
1.7 Gonadotoxic chemotherapeutic agents



Notes:

Anthracyclines, platinum agents, and topoisomerase inhibitors are thought to carry a moderate risk of gonadotoxicity. Doxorubicin is an anthracycline often used to treat lymphomas, leukemia, breast cancer and sarcomas. Platinum agents such as cisplatin and carboplatin are frequently used in the treatment of gynecologic malignancies. Etoposide is a topoisomerase II inhibitor which is used to treat lung cancer, stomach cancer and non-Hodgkin lymphoma.

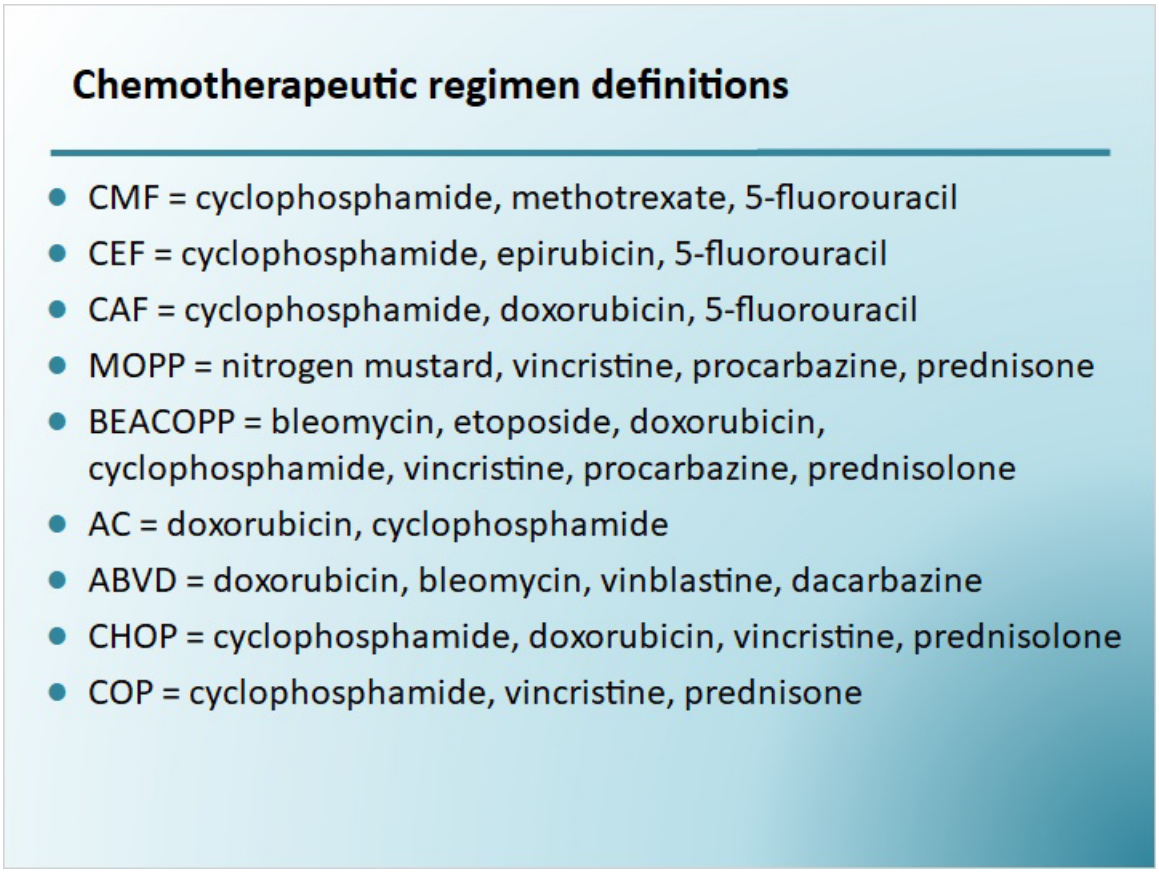
1.8 Gonadotoxic chemotherapeutic agents



Notes:

Antimetabolites and vinca alkaloids are typically associated with a low risk of gonadotoxicity. Methotrexate is a folate antagonist often used to in the treatment of hematologic malignancies and non-malignant conditions such as rheumatoid arthritis. Another example is 5-fluorouracil which irreversibly inhibits thymidylate synthase and is often used to treat colon and skin cancers. While these agents can induce DNA strand breaks, they are not associated with a significant risk of gonadotoxicity. Vincristine, a vinca alkaloid, is commonly used to treat Hodgkin lymphoma and is similarly associated with a low risk of gonadotoxicity.

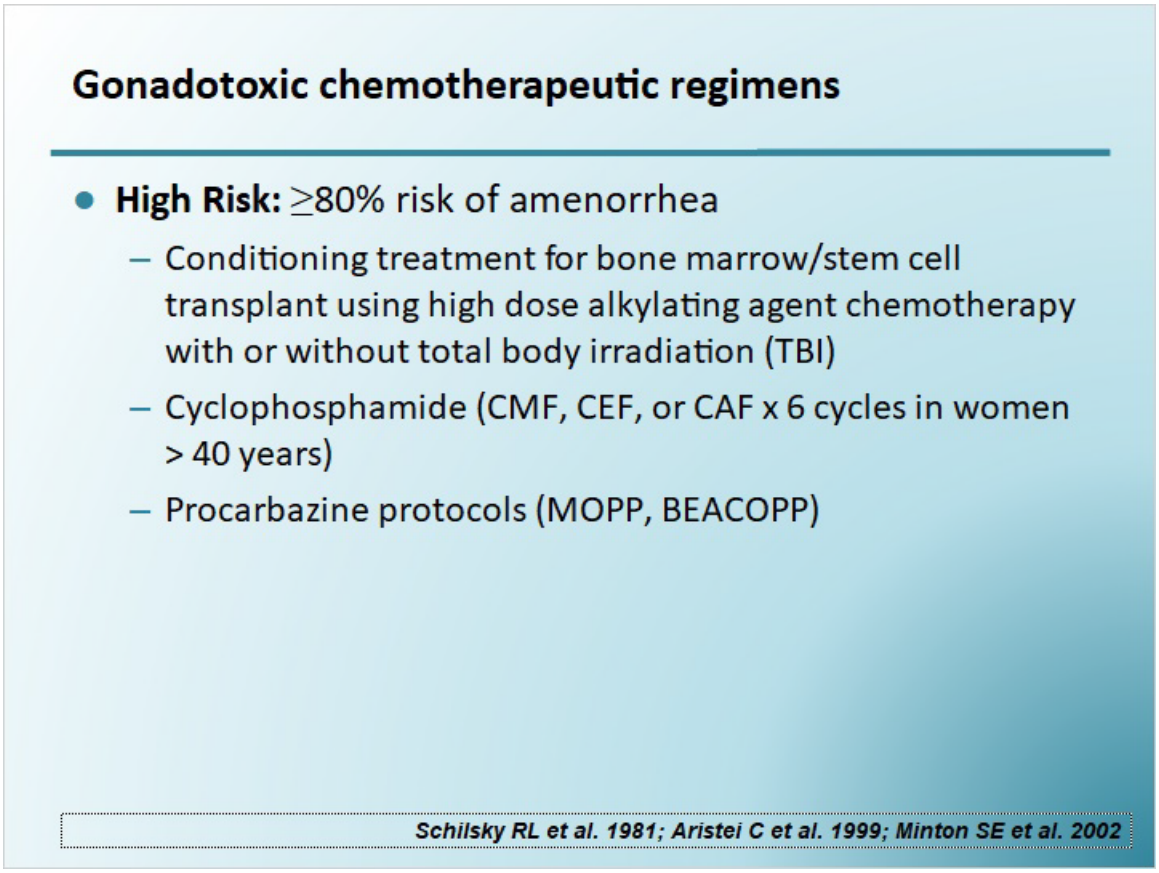
1.9 Chemotherapeutic regimen definitions



Notes:

Many chemotherapeutic agents are used in combination as part of common multi-drug regimens that are described by a single acronym. This slide defines the agents involved in several regimens that will be referred to by acronym in the upcoming slides.

1.10 Gonadotoxic chemotherapeutic regimens

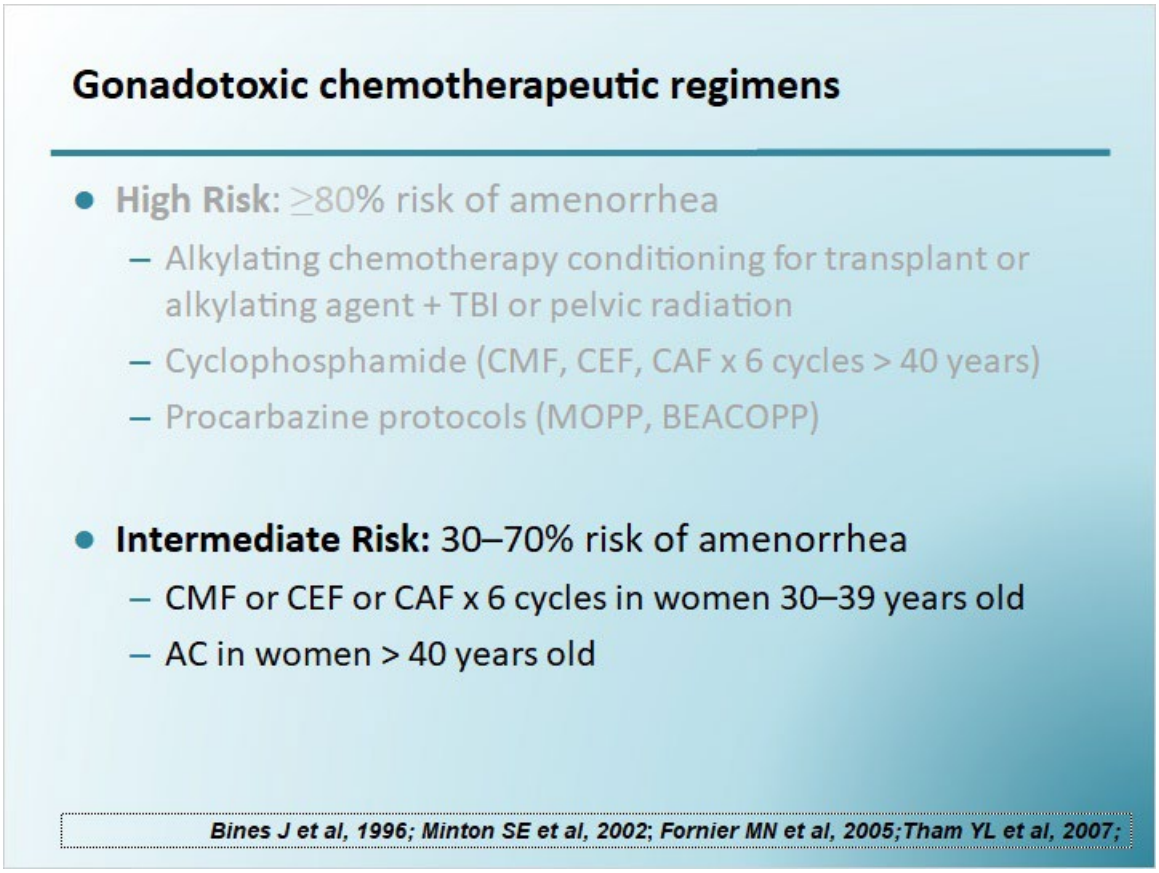


Notes:

Women facing stem cell transplant for certain leukemias or lymphomas are at high risk for developing amenorrhea due to the alkylating agents and radiation given for pre-transplant conditioning. Total body irradiation (TBI) is typically used in conditioning regimens prior to bone marrow transplantation (BMT). This serves to provide both immuno - and myelosuppressive effects and to create space in the bone marrow for transplanted cells to engraft. However, total body irradiation is not always used prior to autologous stem cell transplantation (ASCT) if immunosuppression is not absolutely required.

Higher doses of cyclophosphamide in regimens previously used to treat breast cancer such as CMF, CEF and CAF were associated with high rate of amenorrhea in women over 40 years of age. Similarly, the alkylating agent procarbazine which was previously used to treat Hodgkin lymphoma in the regimen MOPP was associated with a higher risk of amenorrhea. The regimen BEACOPP also includes procarbazine and is currently used as an alternative treatment for advanced or unfavorable Hodgkin lymphoma.

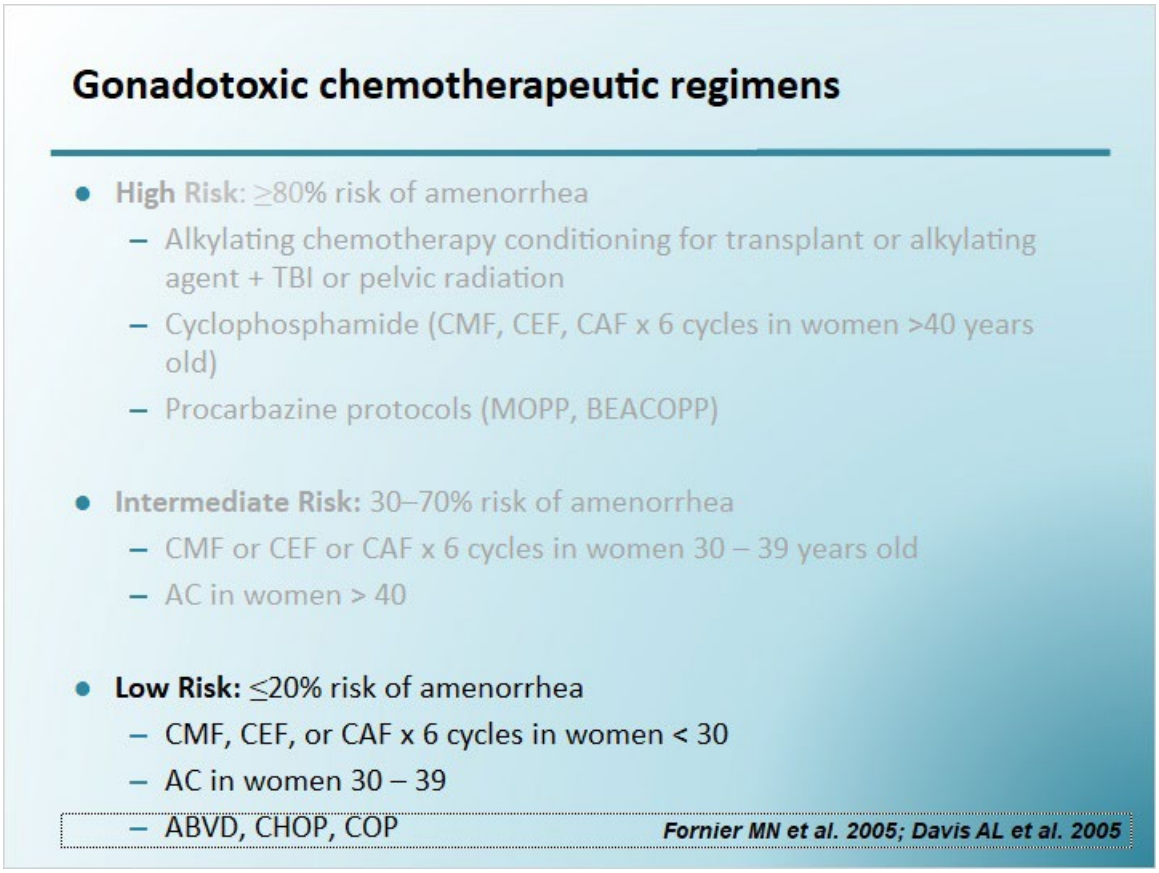
1.11 Gonadotoxic chemotherapeutic regimens



Notes:

Higher doses of cyclophosphamide in regimens previously used to treat breast cancer such as CMF, CEF and CAF were associated with intermediate risks of amenorrhea in women ages 30-39. The current regimen commonly used to treat breast cancer is called AC and includes the moderately gonadotoxic agent doxorubicin and a lower dose of cyclophosphamide. Women over the age of 40 treated with AC are at intermediate risk for developing amenorrhea.

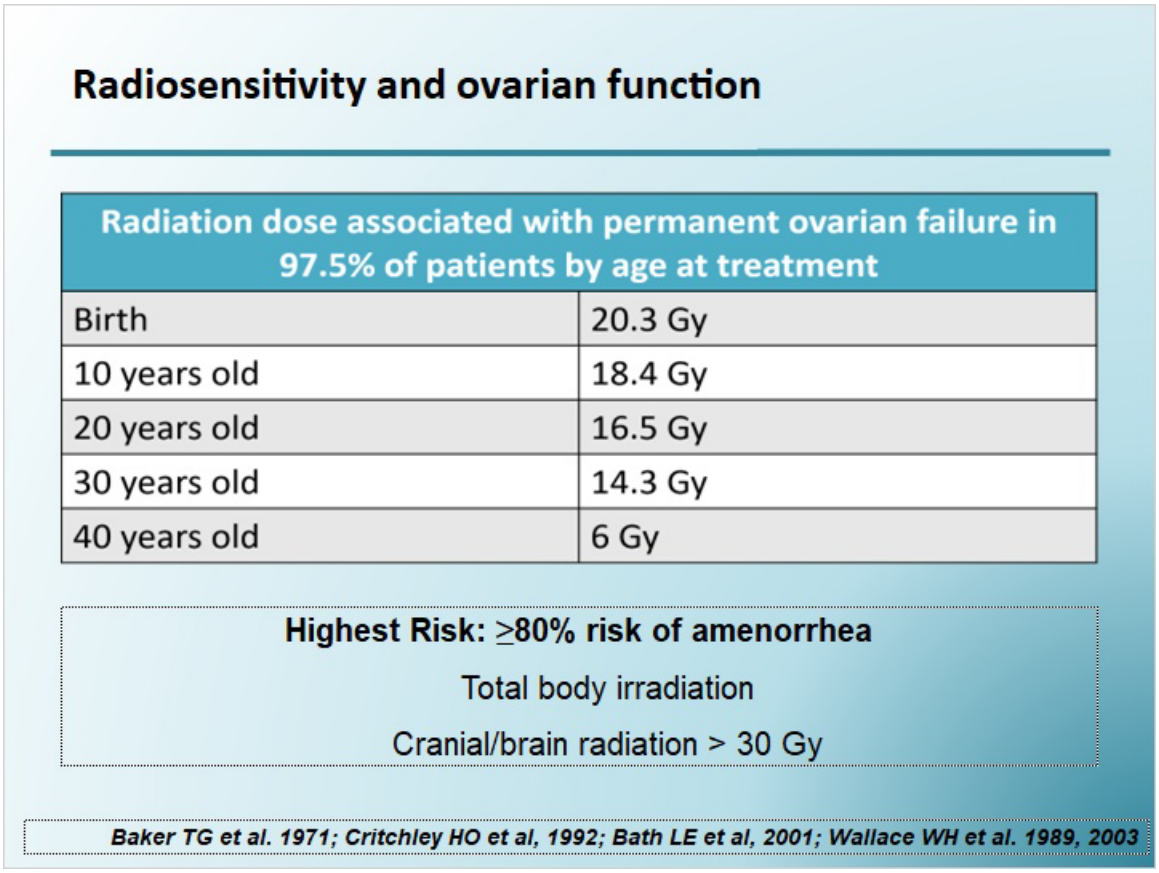
1.12 Gonadotoxic chemotherapeutic regimens



Notes:

The use of the cyclophosphamide containing regimens previously or currently used to treat breast cancer are associated with lower risk of amenorrhea among younger women. Treatment for Hodgkin lymphoma have been replaced with the less gonadotoxic regimens called ABVD, CHOP and COP.

1.13 Radiosensitivity and ovarian function



Notes:

Human oocytes are generally more sensitive to the direct effects of ovarian radiation when compared to the gonadotoxic effects of most chemotherapeutic agents. Radiation damage to the germ cells is both age and dose dependent. Younger women, having greater ovarian reserve, require a higher radiation dose to achieve ovarian failure when compared to older women. A 20-year-old female can experience ovarian failure with 16.5 Gy exposure whereas a 40-year-old can experience ovarian failure with radiation doses as low as 6 Gy. Prepubertal radiation exposure may result in delayed puberty and primary amenorrhea. Secondary amenorrhea and menopausal symptoms due to ovarian failure may occur with post pubertal radiation exposure.

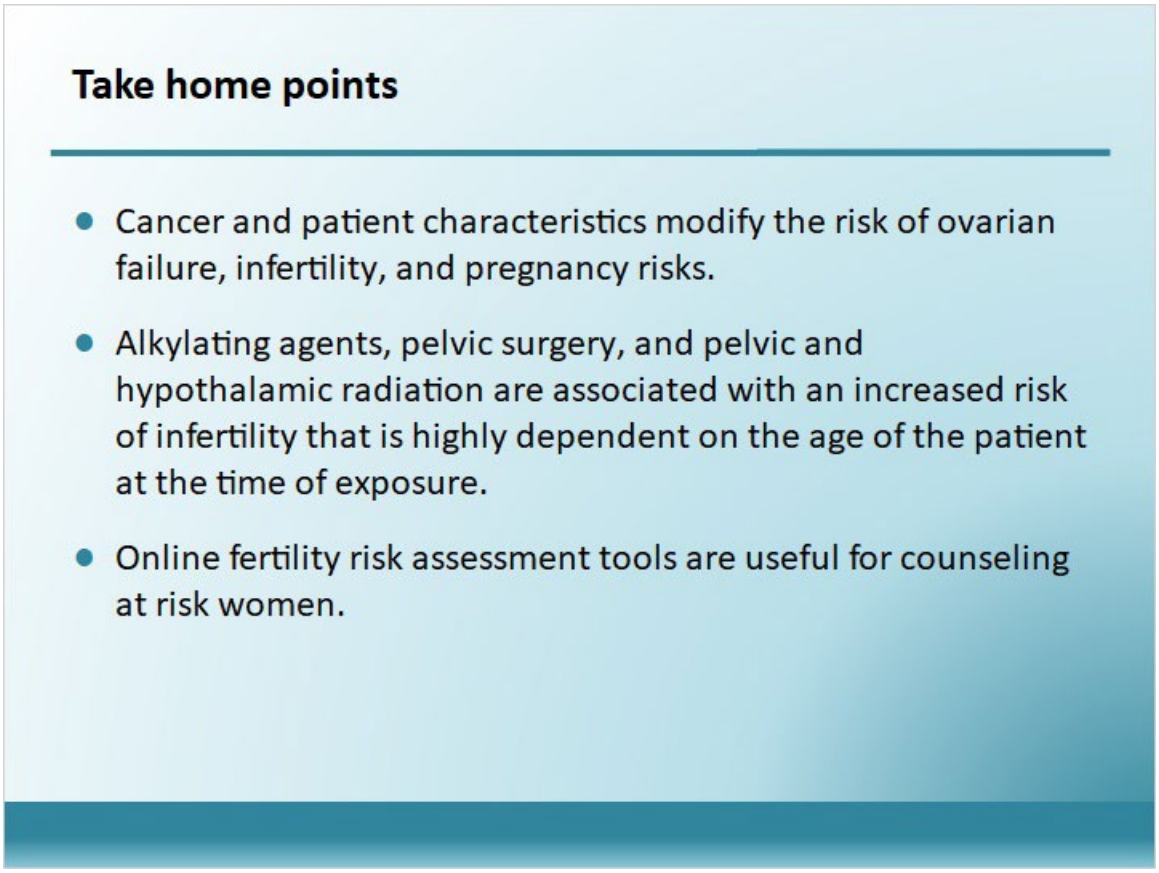
Total body irradiation, typically used in preconditioning regimens for bone marrow transplant, is particularly gonadotoxic with a >80% risk of amenorrhea. Cranial irradiation in excess of 30 Gy may cause delayed damage to the hypothalamic - pituitary region, eventually leading to a similarly high rate of hypothalamic amenorrhea in women. In addition to the impact on ovarian function, total body, abdominal, or pelvic radiation has also been associated with significantly reduced uterine volume and a raised incidence of intrauterine growth retardation and spontaneous miscarriage.

1.14 Online fertility risk assessment tools

Notes:

When faced with counseling patients regarding the short-term and long-term reproductive consequences of cancer treatments, LIVESTRONG Fertility provides a fertility risk assessment tools that can estimate the risk of post-treatment amenorrhea for various chemotherapies or radiation exposure. In addition, the Oncofertility Consortium website provides valuable information regarding pregnancy risks. These tools can assist with generating an individualized risk assessment based on age, cancer diagnosis, treatment and future fertility goals.

1.15 Take home points



Notes:

In summary, cancer and patient characteristics modify the risk of ovarian failure, infertility, and pregnancy risks. Alkylating agents, pelvic surgery, and pelvic and hypothalamic radiation are associated with an increased risk of infertility that is highly dependent on the age of the patient at the time of exposure. Finally, there are online fertility risk assessment tools that are useful for counseling at-risk women.

1.16 Thank you!

Notes:

Thank you for your participation. We hope you enjoyed the course.