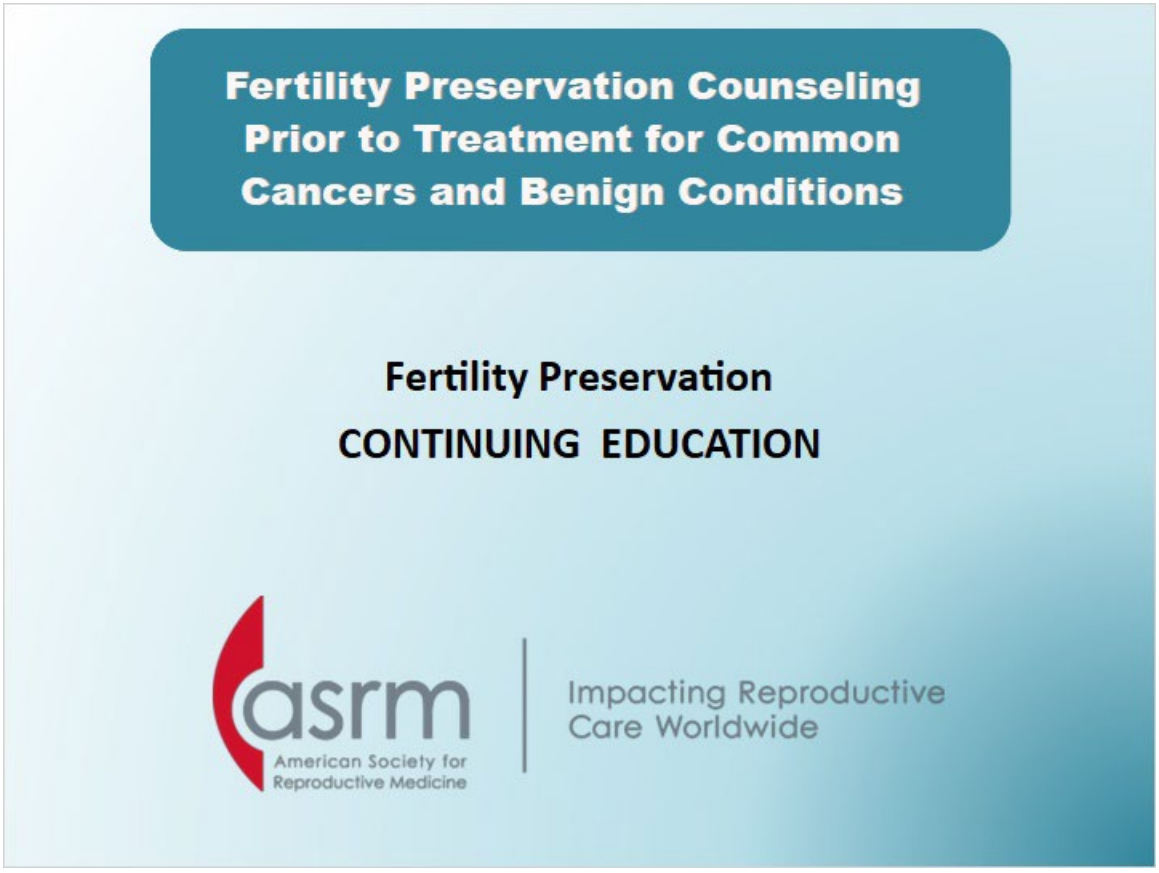
MD120 Lesson 3

1. MD120_L3

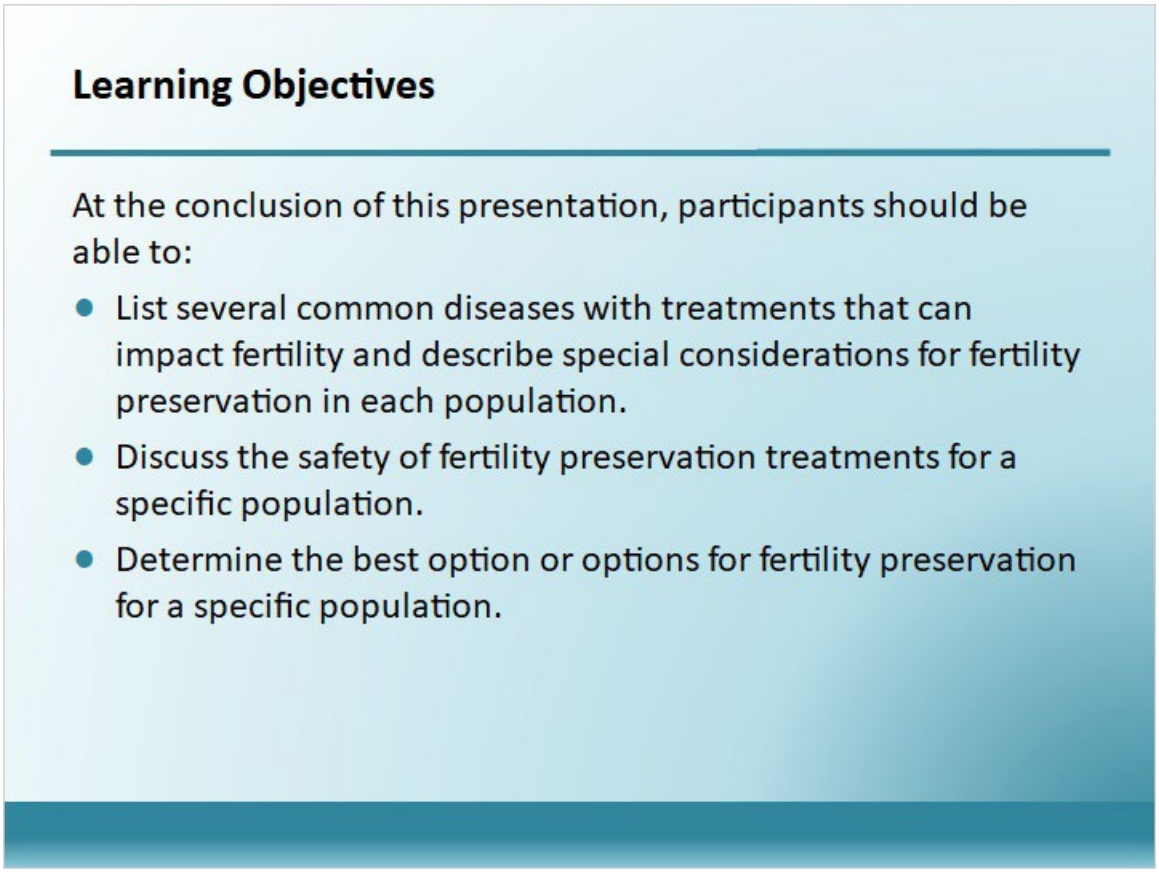
1.1 Fertility Preservation Counseling Prior to Treatment for Common Cancers and Benign Conditions



Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Fertility preservation counseling prior to treatment for common benign and malignant conditions."

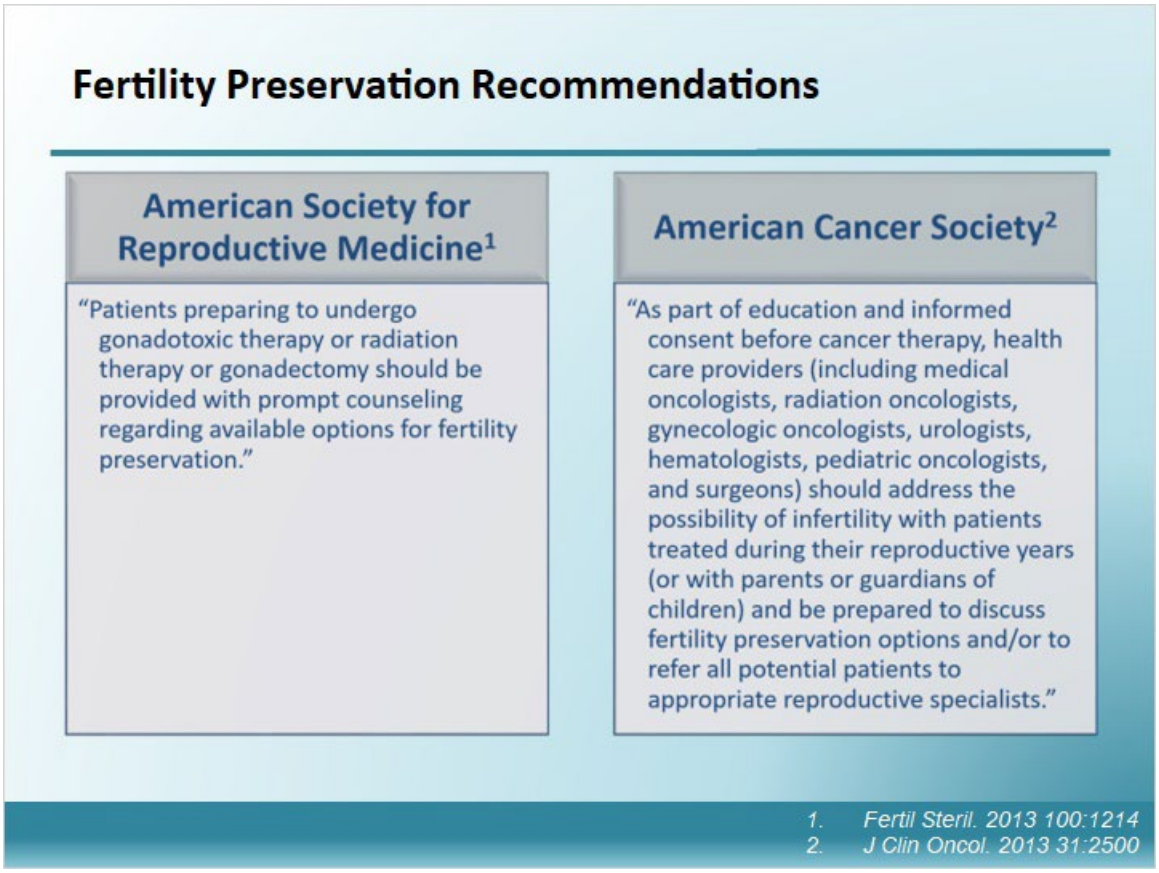
1.2 Learning Objectives



Notes:

At the conclusion of this presentation, participants should be able to:
1. List several common diseases with treatments that can impact fertility and describe special considerations for fertility preservation in each population.
2. Discuss the safety of fertility preservation treatments for a specific population.
3. Determine the best option or options for fertility preservation for a specific population.

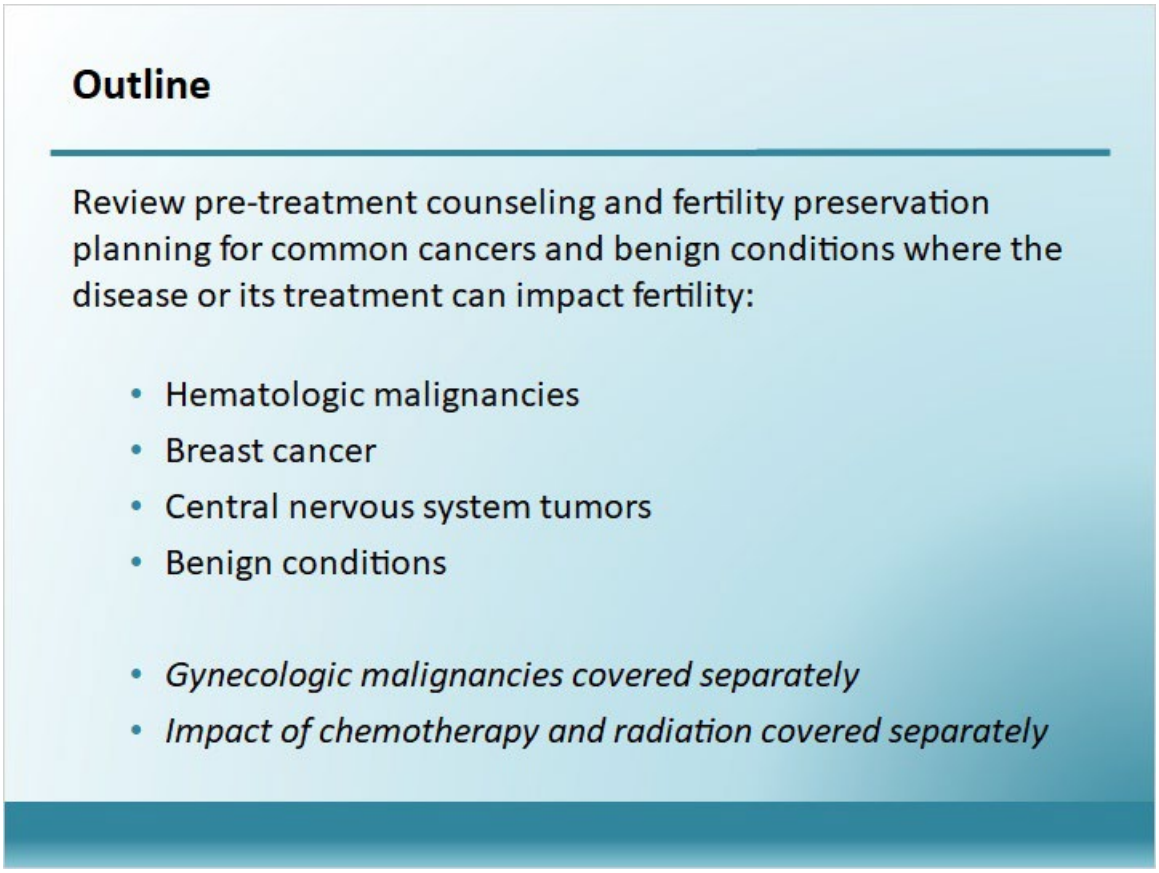
1.3 Fertility Preservation Recommendations



Notes:

Both the American Cancer Society and the American Society for Reproductive Medicine have formal opinions that patients whose conditions place them at risk for infertility should be offered fertility preservation prior to proceeding with chemotherapy or radiation therapy.

1.4 Outline

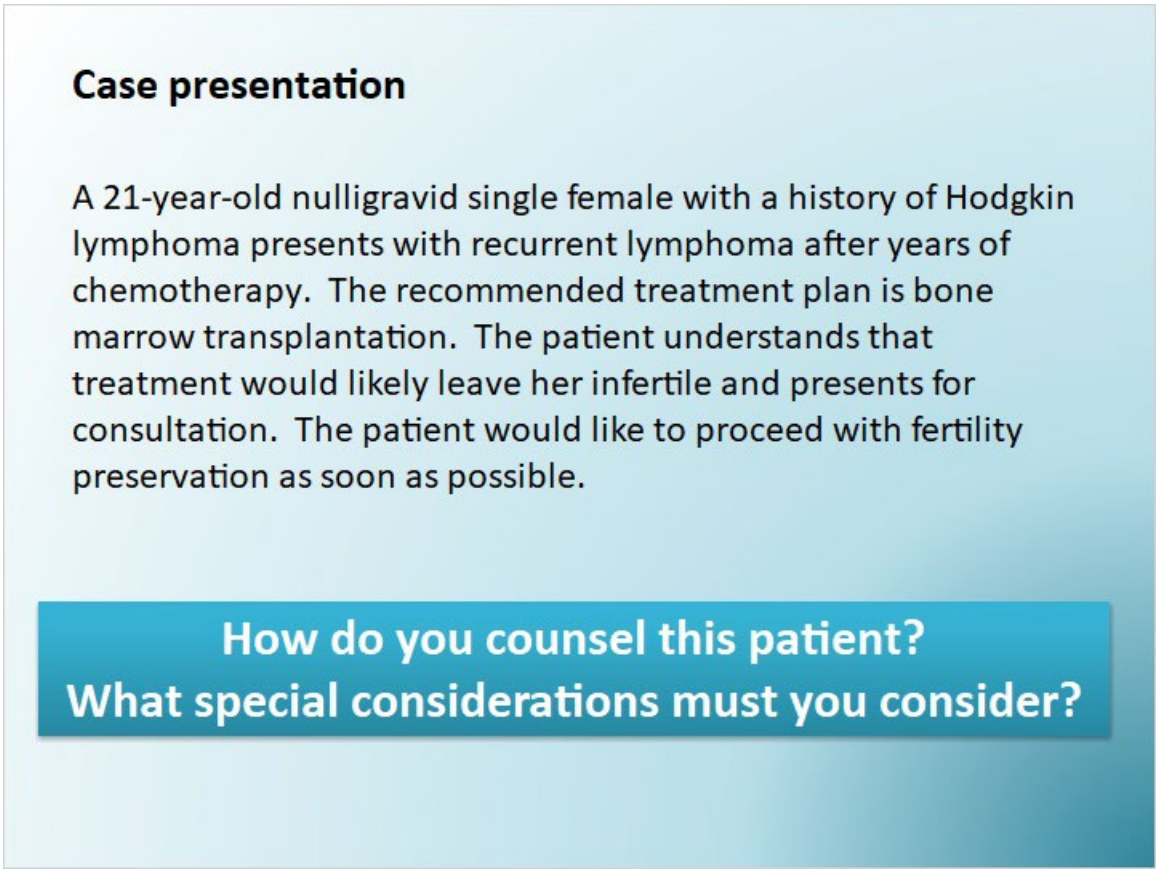


Notes:

This module will review pre-treatment counseling and fertility preservation planning for several conditions where the disease or its treatment can impact fertility-including hematologic malignancies, breast cancer, central nervous system tumors, and benign conditions. The module will review special considerations for each condition separately, explore and discuss safety concerns associated with different fertility preservation techniques, and provide information to help choose the best option for future fertility in each condition.

Gynecologic malignancies represent a significant proportion of cancers in women of reproductive age and will be covered in detail in a separate module. The impact of chemotherapy and radiation on fertility is likewise covered in detail in a separate module.

1.5 Case presentation



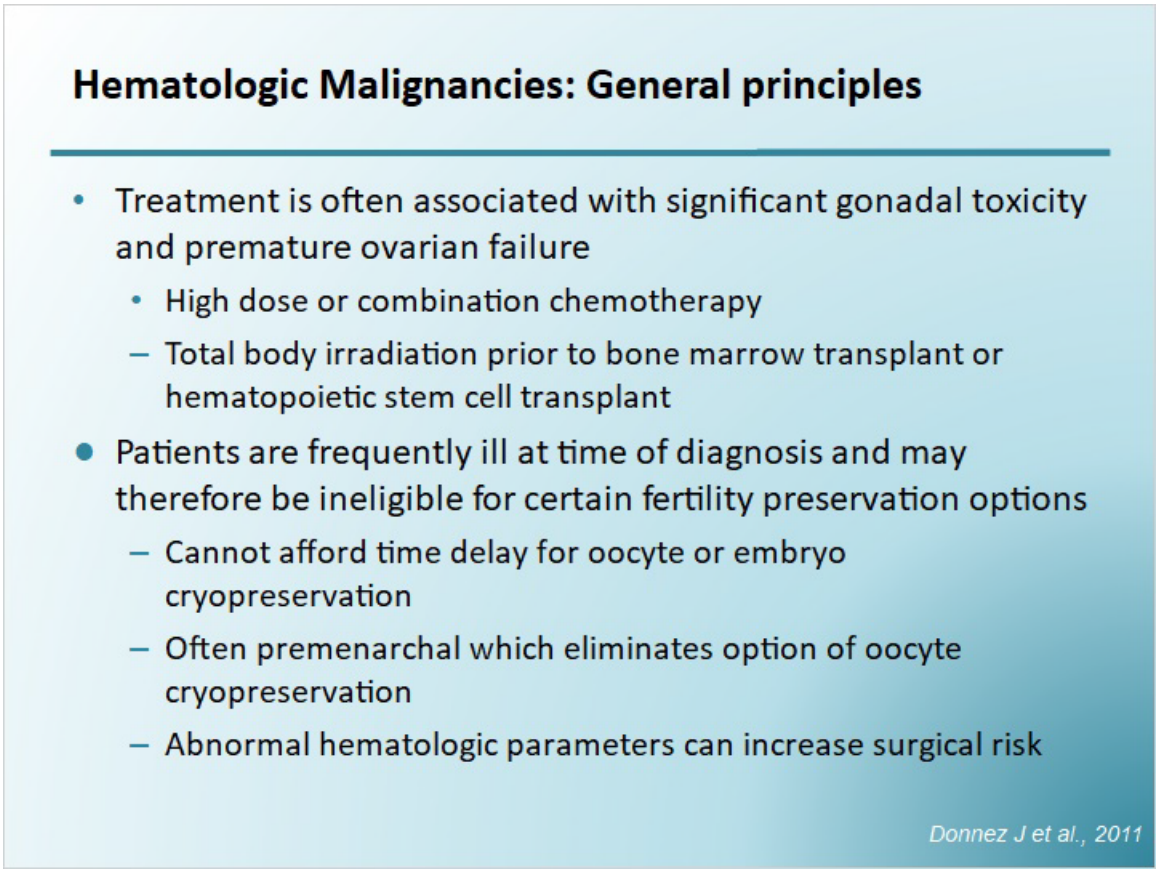
Notes:

We will start each section with a case presentation.
A 21-year-old nulligravid single female with a history of Hodgkin lymphoma presents with recurrent lymphoma after years of chemotherapy. The recommended treatment plan is bone marrow transplantation. The patient understands that treatment would likely leave her infertile and presents for consultation. The patient would like to proceed with fertility preservation as soon as possible.

How do you counsel this patient?

What special considerations must you consider?

1.6 Hematologic Malignancies: General principles



Notes:

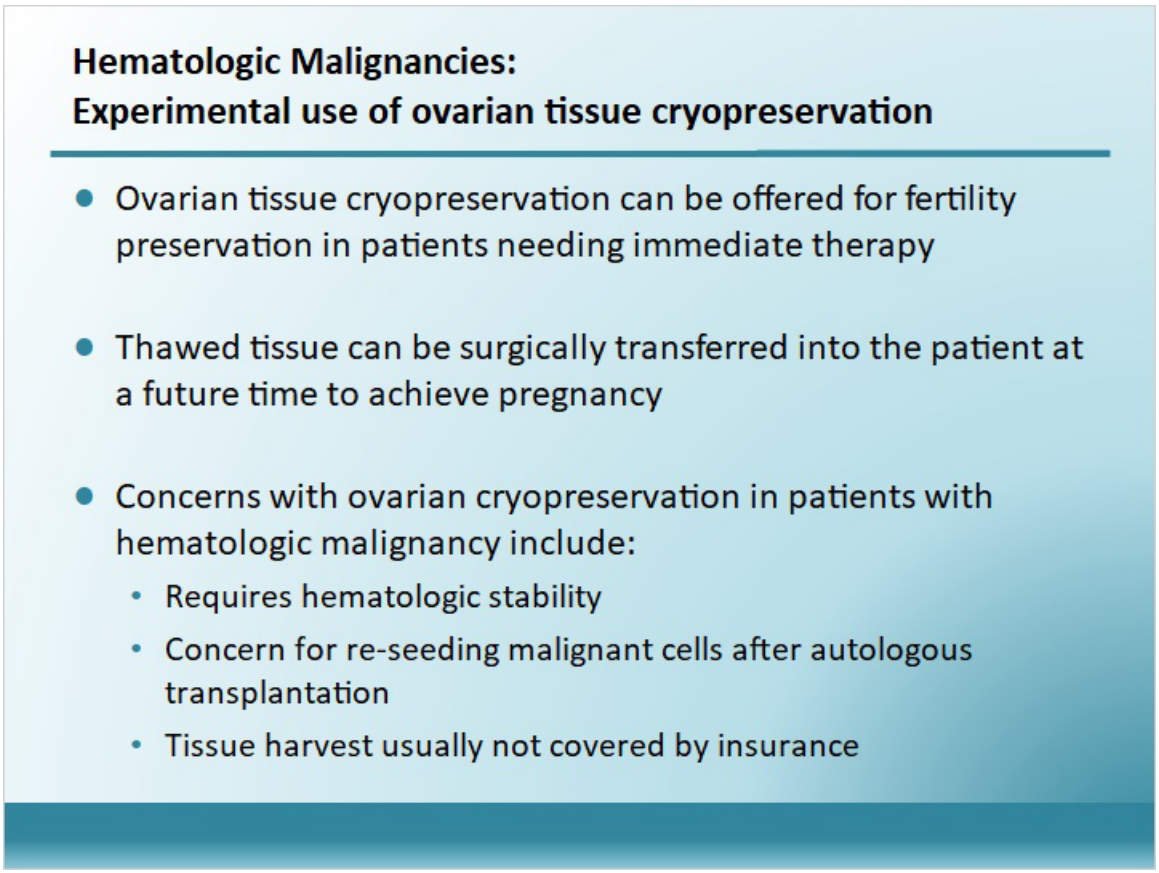
Hematologic malignancies are among the most common cancers causing patients to seek consultation for fertility preservation. The most common conditions include Hodgkin and non-Hodgkin lymphoma, and leukemia.

Patients with hematologic malignancies can present unique challenges in counseling and management of fertility preservation. Leukemia and some lymphomas are frequently treated with highly toxic chemotherapy regimens that may be multi-agent and include high doses of alkylating agents such as cyclophosphamide. Some of these patients will require bone marrow transplant or hematopoietic stem cell transplant preceded by total body irradiation. Patients in these situations are at high risk of fertility compromise and premature ovarian failure.

An additional consideration is that many patients can be very ill at the time they receive a cancer diagnosis. These individuals may not have time to delay treatment to undergo ovarian stimulation for oocyte or embryo cryopreservation. Patients are often premenarchal, which eliminates the option of oocyte or embryo cryopreservation since eggs cannot be retrieved. Moreover, abnormal hematologic parameters may lead to

increased risk of bleeding during surgical procedures such as transvaginal oocyte aspiration.

1.7 Hematologic Malignancies:



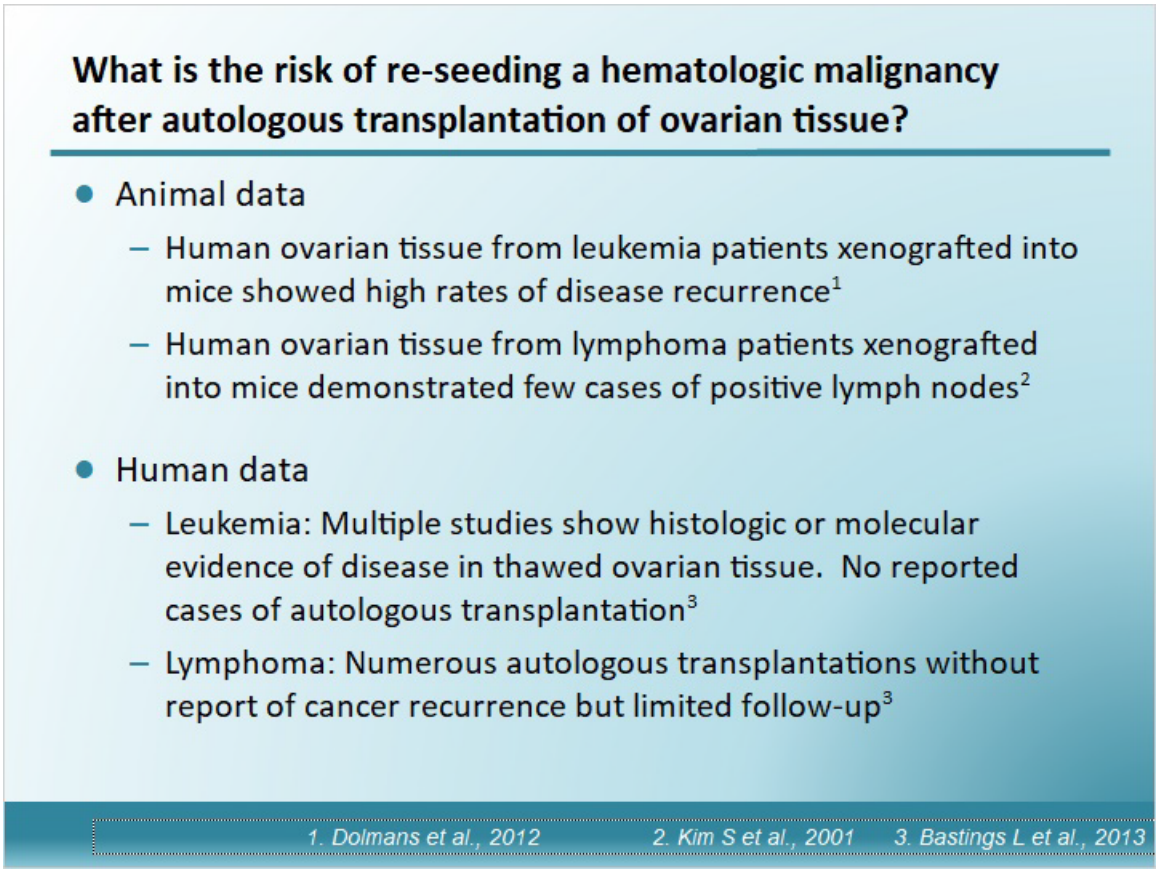
Notes:

Ovarian tissue cryopreservation is a currently experimental method of fertility preservation in prepubertal girls but can also be offered to reproductive-age women who cannot afford the time delay associated with controlled ovarian stimulation. Ovarian tissue cryopreservation involves surgical removal**,** usually by laparoscopy, of a portion or a complete ovary with cryopreservation of cortical strips for future use. When the patient's medical condition permits, the ovarian tissue is thawed and transplanted into the ovarian fossa where folliculogenesis can resume. Several pregnancies have resulted from this treatment to date.

Though not having to wait two weeks for ovarian stimulation is an obvious benefit of this approach, several concerns exist regarding its use in patients with hematologic malignancies. First, patients must be in adequate health to tolerate the surgical removal

of ovarian tissue. Secondly, autologous transplantation raises concern for re-seeding malignant cells that may persist within the ovarian tissue. Finally, tissue harvest is usually not covered by insurance therefore it is ideal if the procedure can be done in conjunction with another procedure that is covered by insurance and requires general anesthesia.

1.8 What is the risk of re-seeding a hematologic malignancy after autologous transplantation of ovarian tissue?



Notes:

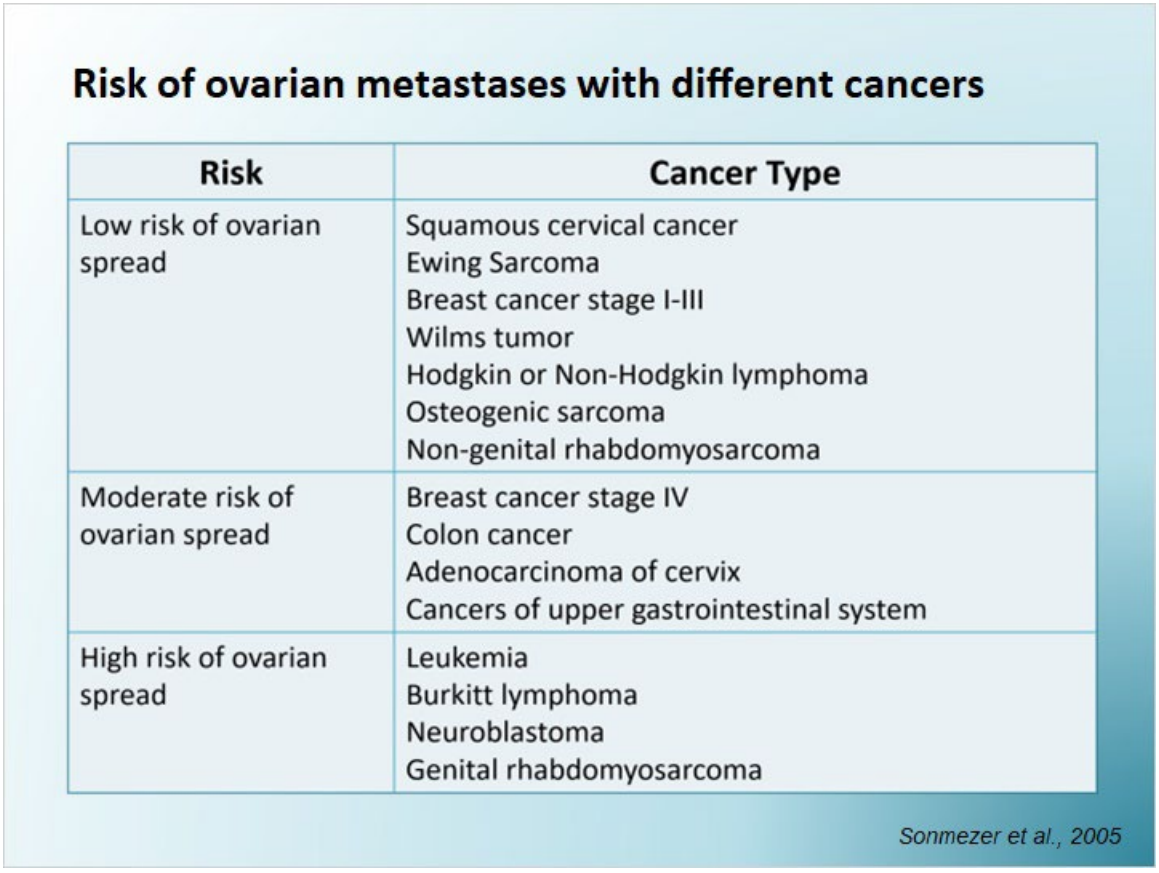
Several studies both in animals and humans have addressed the risk of re-seeding malignant cells during autologous transplantation of ovarian tissue.

Ovarian tissue from leukemic patients (including acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML) has been xenografted into murine models to study risk of disease recurrence. Markers of residual cancer were identified in 7 of 10 mice exposed to ALL and 2 of 6 mice exposed to CML. Four mice developed intra-abdominal

tumors. A similar experiment using tissue from lymphoma patients found positive lymph nodes in 2 of 5 mice after xenografting ovarian tissue from patients with Non-Hodgkin lymphoma but no positive lymph nodes after xenografting ovarian tissue from patients with Hodgkin lymphoma.

Human studies using histologic and molecular testing found high rates of residual disease in ovarian tissue of leukemia patients. Given this risk, no cases of autologous transplantation in leukemia patients have been reported. In contrast, autologous transplantation of ovarian tissue has been reported in several patients with lymphoma without report of disease recurrence, though long-term follow up is limited to date.

1.9 Risk of ovarian metastases with different cancers

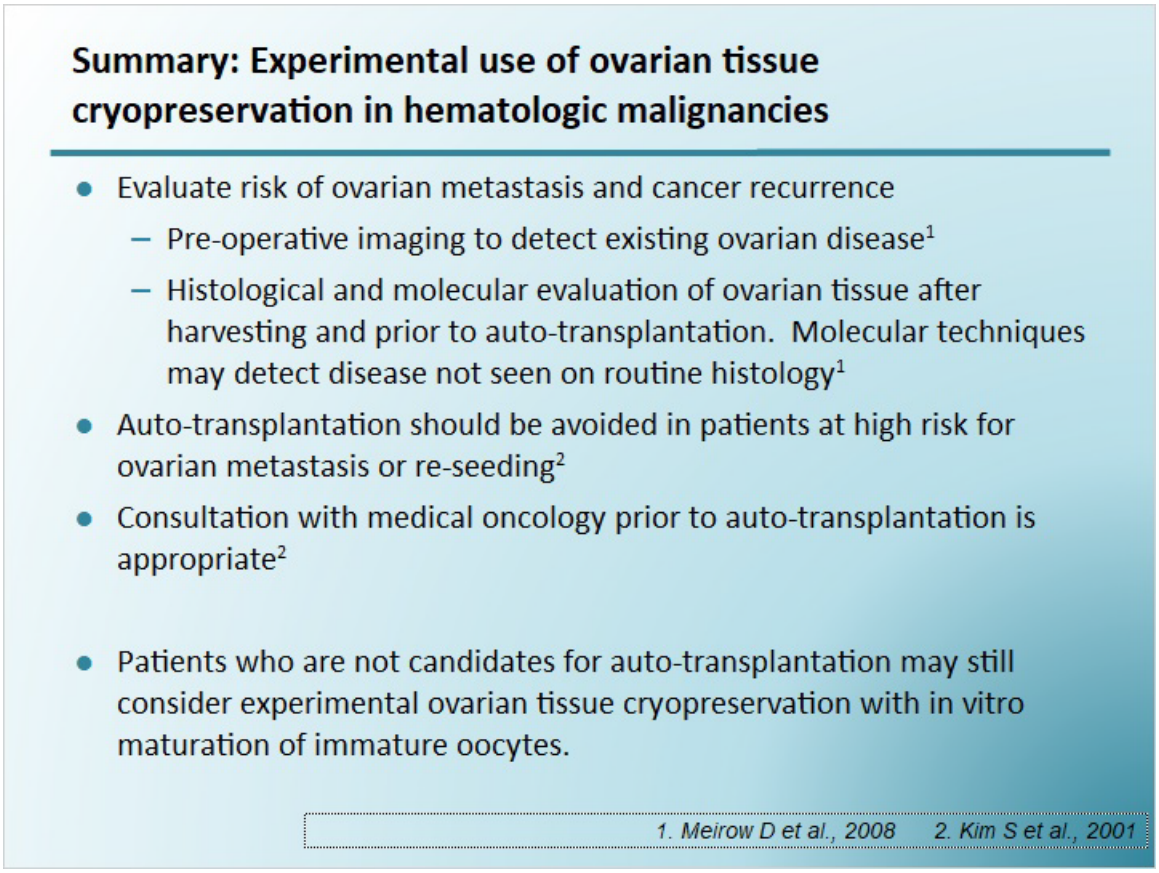


Notes:

It is important to recognize that the high risk of re-seeding cancer identified with autologous transplantation of ovarian tissue in leukemic patients does not apply for all malignancies. Many cancers, including Hodgkin and Non-Hodgkin lymphoma, carry a very low risk of ovarian spread leaving ovarian tissue cryopreservation as an option for

fertility preservation. Stage IV breast cancer and gastrointestinal malignancies carry moderate risk, whereas risk is highest for leukemia, Burkitt lymphoma, neuroblastoma, and genital rhabdomyosarcoma.

1.10 Summary: Experimental use of ovarian tissue cryopreservation in hematologic malignancies



Notes:

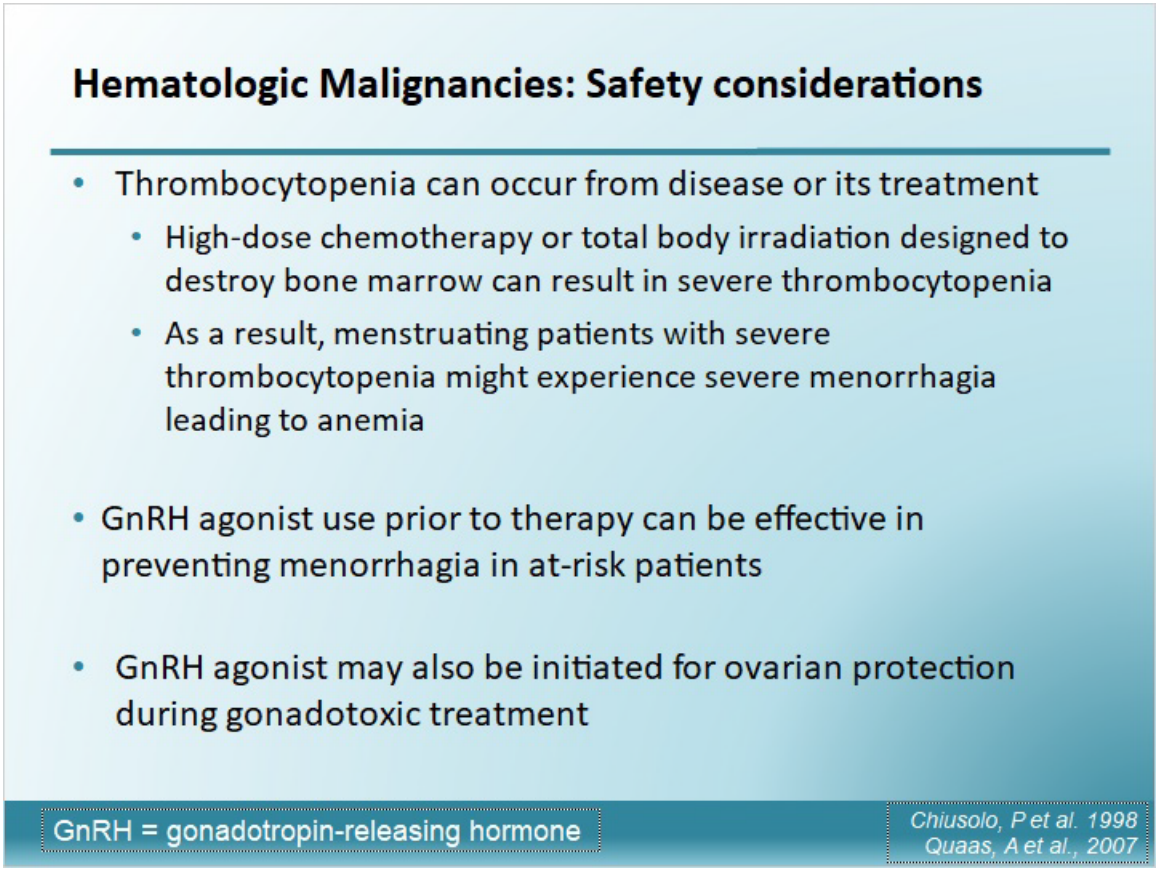
In summary, pre-treatment counseling for use of ovarian tissue cryopreservation for fertility preservation in patients with hematologic malignancies should consider several points.

The risk of ovarian metastasis and the possibility of re-seeding cancer during autologous transplantation should be discussed and evaluated. Pre-operative imaging studies including ultrasound and CT scan can provide evidence of ovarian disease and eliminate the unnecessary surgical risk of oophorectomy in these patients. Careful histologic and molecular examination -- including immuno-histochemistry, polymerase chain reaction

(PCR) or real-time PCR -- can detect minimal residual disease within ovarian tissue and should be considered after harvesting and before autologous transplantation. Consultation and coordination with medical oncology is vital and recommended prior to autologous transplantation of ovarian tissue.

Patients who are not candidates for autologous transplantation of ovarian tissue may still consider experimental ovarian tissue cryopreservation. Immature oocytes have been collected and matured in vitro to metaphase II prior to vitrification, although long-term outcome data are not yet available. Additionally, several groups continue to research potential future uses for ovarian tissue without autologous transplantation. Patients and families must clearly understand the experimental nature of these options and the limited data on their use.

1.11 Hematologic Malignancies: Safety considerations



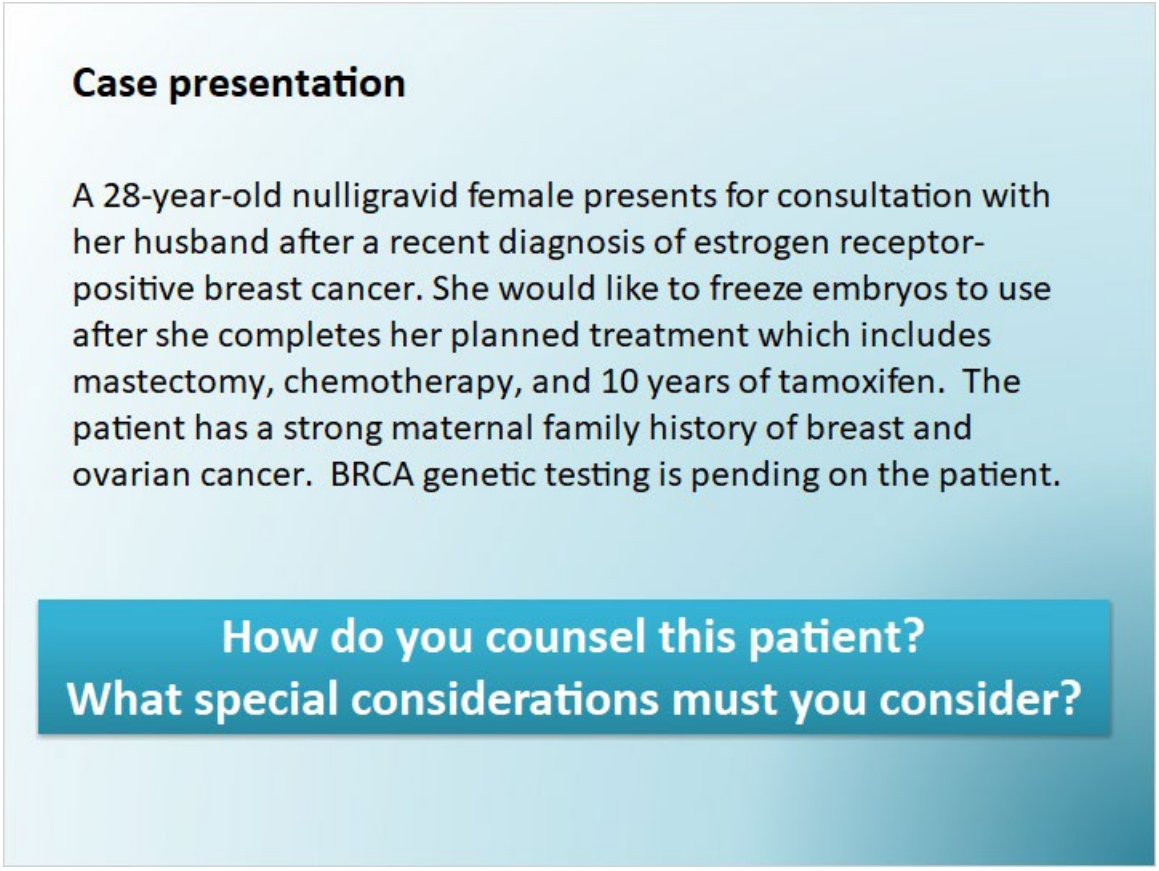
Notes:

In addition to their impact on fertility, hematologic malignancies and/or their treatment can profoundly increase the risk of bleeding in a patient. High dose chemotherapy or

total body irradiation are designed to destroy bone marrow prior to bone marrow transplant or hematopoietic stem cell transplant. Menstrual bleeding can result in severe menorrhagia and anemia in thrombocytopenic patients. Ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists has been advocated to prevent menorrhagia in at-risk patients. GnRH agonists appear to be more effective than continuous combined oral contraceptives or injectable medroxyprogesterone acetate due to the higher rates of breakthrough bleeding with the latter two regimens. Although controversial, GnRH agonists can be used for ovarian protection during gonadotoxic treatment although current literature has not shown proven benefit in hematologic malignancies to prevent post-treatment amenorrhea. If using a GnRH agonist for this purpose a provider should explain the experimental nature of this therapy and all risks, benefits, and alternatives.

The use of GnRH agonists in fertility preservation is covered in greater detail in a separate module in this series.

1.12 Case presentation



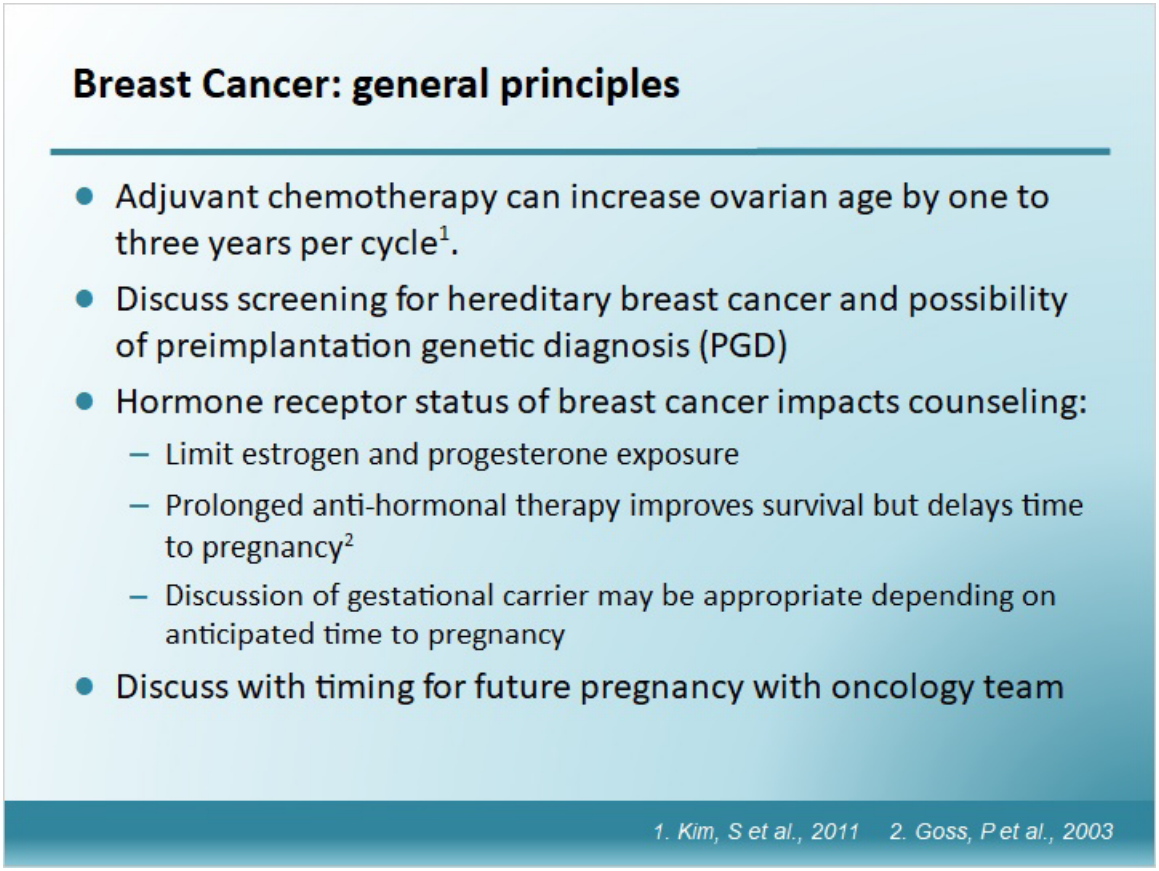
Notes:

A 28-year-old nulligravid female presents for consultation with her husband after a recent diagnosis of estrogen receptor-positive breast cancer. She would like to freeze embryos to use after she completes her planned treatment which includes mastectomy, chemotherapy, and five years of tamoxifen. The patient has a strong maternal family history of breast and ovarian cancer. BRCA genetic testing is pending on the patient.

How would you counsel this patient?

What special considerations must you consider?

1.13 Breast Cancer: general principles



Notes:

Breast cancer is among the most common cancers in reproductive aged women, and is therefore a frequent condition encountered during fertility preservation consultations. Several principles should be considered when evaluating breast cancer patients interested in future fertility, many of which will be elaborated upon in the following slides.

Chemotherapy for breast cancer is frequently gonadotoxic and can result in significant oocyte

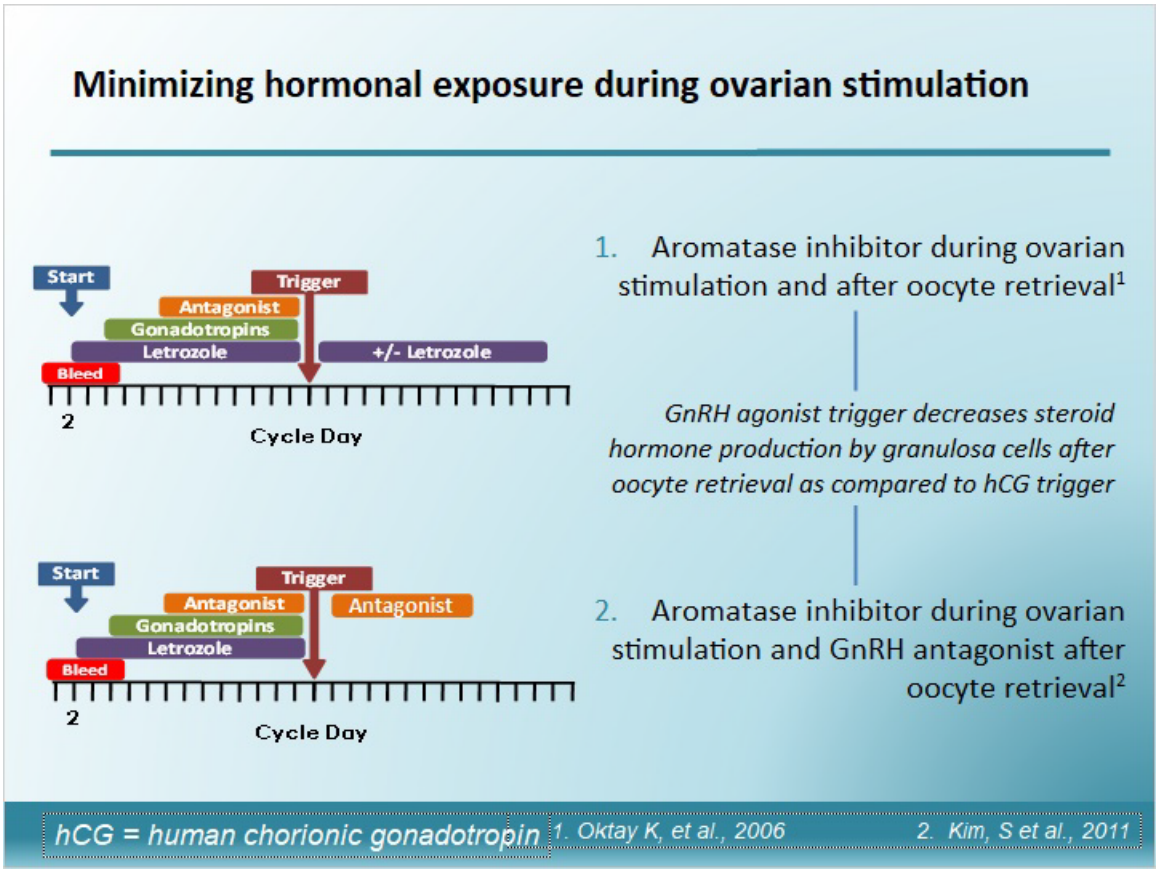
loss. Alkylating agents such as cyclophosphamide have been reported to increase ovarian age by 1 to 3 years per cycle.

Most breast cancers are sporadic, but rates of hereditary cancer can be higher in women with a strong family history of breast or ovarian cancer. Screening for hereditary breast and ovarian cancer with consideration of pre-implantation genetic diagnosis may be warranted in cases with a suggestive family history.

The hormone receptor status of a patient's breast cancer is of particular relevance to fertility preservation counseling and treatment. Supra-physiologic estrogen and progesterone levels encountered during ovarian stimulation for oocyte or embryo banking can be a concern for women with hormone sensitive breast tumors, and care should be taken to minimize circulating levels of ovarian steroids during treatment. Five to ten years of anti-hormonal therapy with tamoxifen has been shown to improve long-term survival in patients with hormonally sensitive tumors but may also result in a time-delay to pregnancy. Depending upon a woman's age at the time of her diagnosis and the extent of the anticipated time delay, counseling on the use of a gestational carrier may be appropriate.

Finally, any patient planning pregnancy should discuss safety and timing concerns directly with her oncology team.

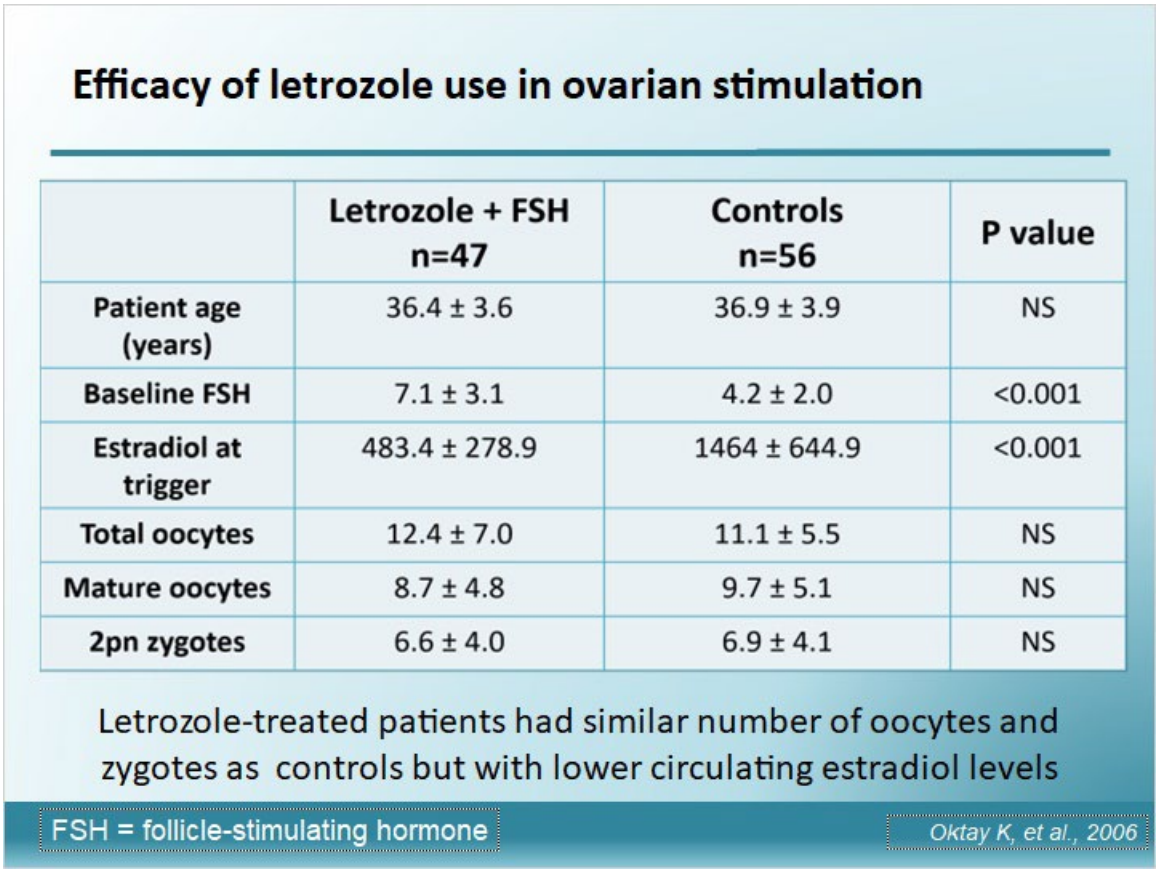
1.14 Minimizing hormonal exposure during ovarian stimulation



Notes:

Several techniques exist to minimize circulating estradiol levels during ovarian stimulation. The first option uses letrozole, an aromatase inhibitor, both during controlled ovarian stimulation and after oocyte retrieval to lower circulating estradiol levels. A second option is to utilize letrozole during ovarian stimulation followed by a GnRH antagonist after oocyte retrieval. In both situations, a GnRH agonist trigger, rather than a standard hCG trigger, can be considered as an additional means to decrease granulosa cell production of estradiol due to the short half-life of endogenous LH over hCG.

1.15 Efficacy of letrozole use in ovarian stimulation

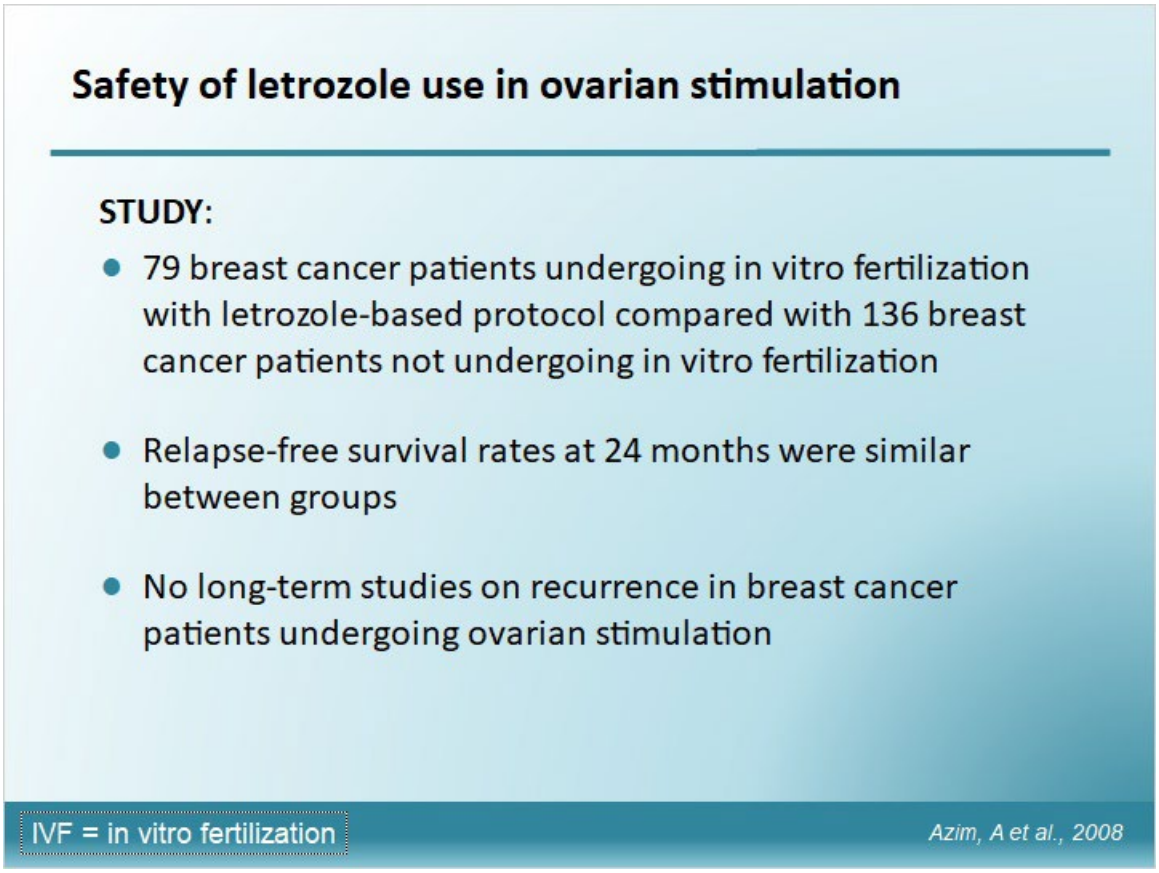


	Letrozole + FSH n=47	Controls n=56	P value
Patient age (years)	36.4 ± 3.6	36.9 ± 3.9	NS
Baseline FSH	7.1 ± 3.1	4.2 ± 2.0	<0.001
Estradiol at trigger	483.4 ± 278.9	1464 ± 644.9	<0.001
Total oocytes	12.4 ± 7.0	11.1 ± 5.5	NS
Mature oocytes	8.7 ± 4.8	9.7 ± 5.1	NS
2pn zygotes	6.6 ± 4.0	6.9 ± 4.1	NS

Notes:

The use of letrozole during ovarian stimulation has been shown to have similar outcome in regards to oocyte and embryo yield when compared with standard protocols. This study compared 47 patients with breast cancer undergoing a letrozole-based protocol to 56 controls utilizing a standard GnRH agonist down-regulation protocol. Demographics of the two study populations were similar other than a higher baseline follicle-stimulating hormone (FSH) value in the breast cancer patients. Numbers of retrieved oocytes and zygotes were similar in both groups, but patients treated with letrozole had significantly lower peak serum estradiol level.

1.16 Safety of letrozole use in ovarian stimulation

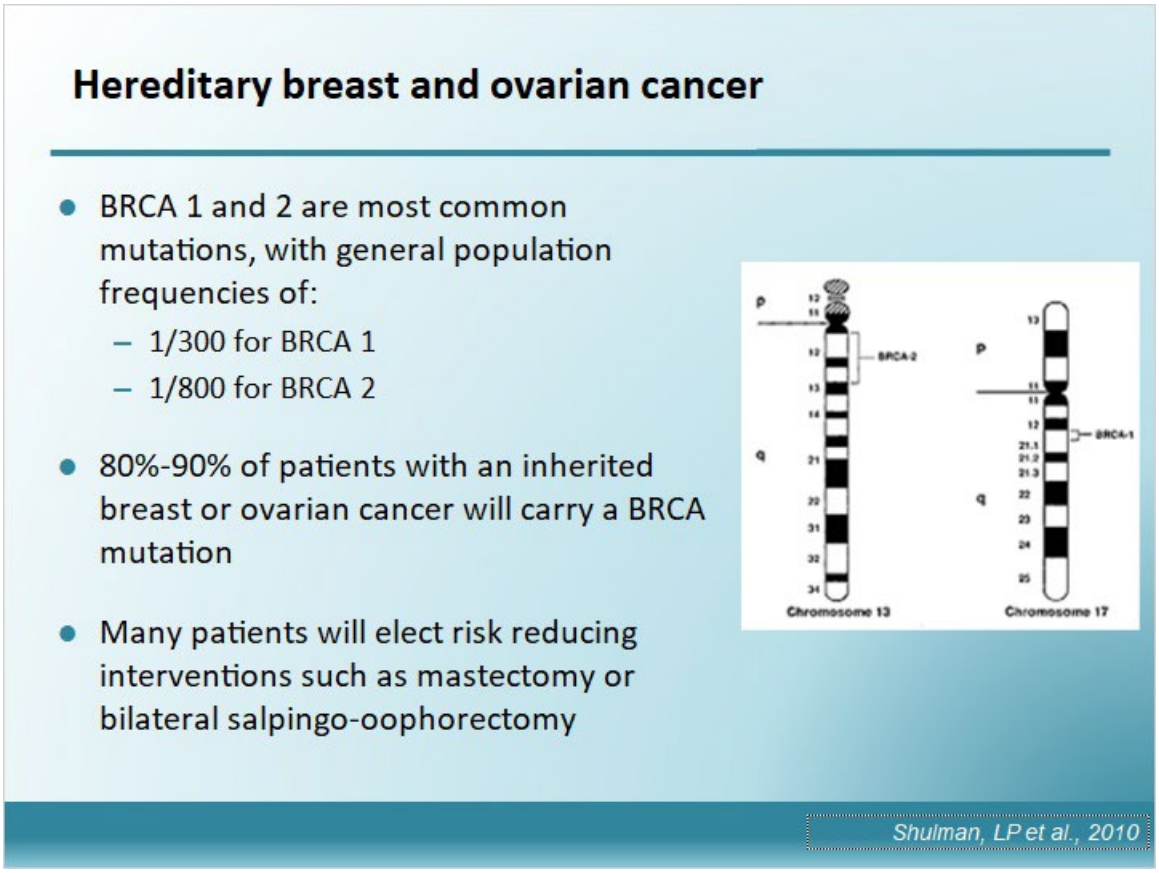


Notes:

Recurrence risk of breast cancer after ovarian stimulation was evaluated in a study comparing 79 breast cancer patients undergoing ovarian stimulation with a letrozole-based protocol to 136 control patients with breast cancer who did not undergo stimulation. Although the ovarian stimulation group had increased time from surgery to initiation of chemotherapy, relapse-free survival was similar between the groups at a median of 2 years of follow up - typically the time period with the highest risk of recurrence.

Ovarian stimulation with letrozole appears to be a safe option for women with breast cancer, though long-term recurrence data are lacking.

1.17 Hereditary breast and ovarian cancer

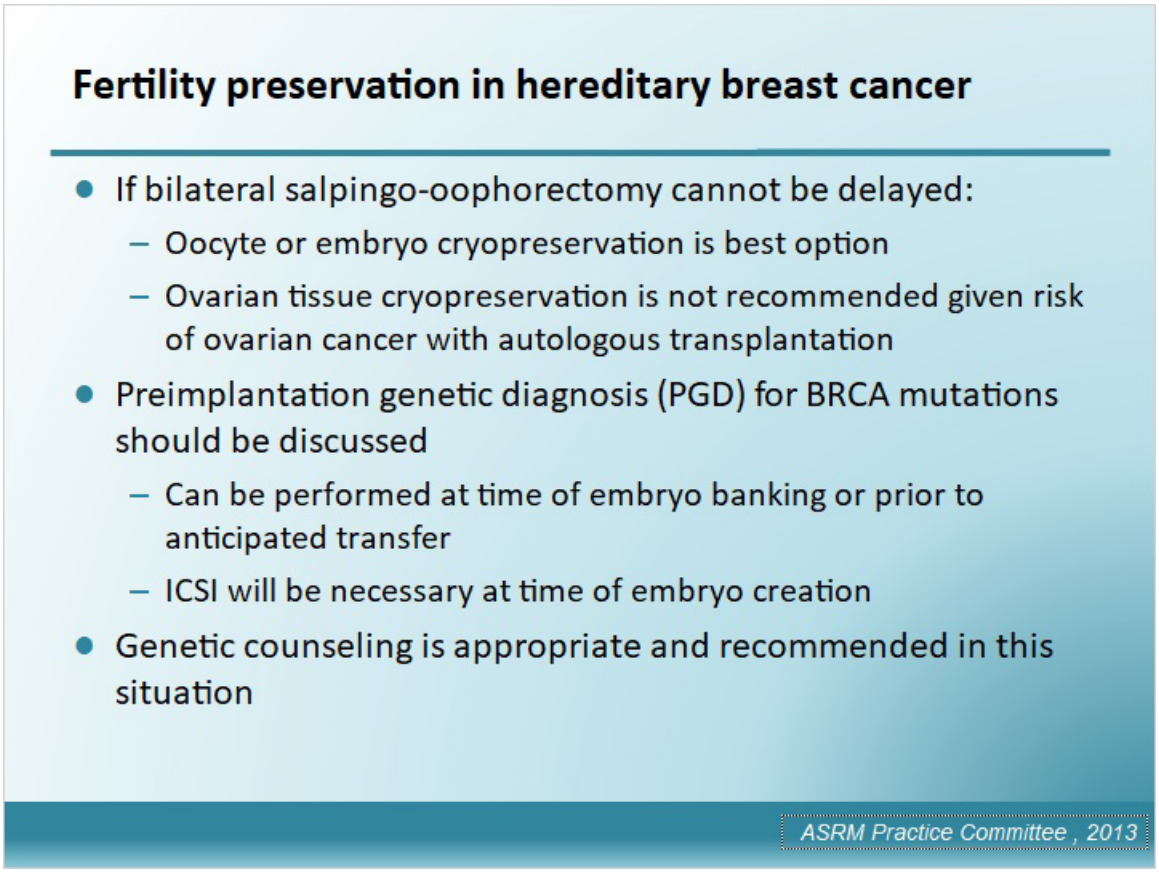


Notes:

Testing for hereditary breast and ovarian cancer is often warranted in younger women with breast cancer, or those with a family history of either disease in multiple relatives. Though the prevalence is low in the general population, a majority of patients with inherited breast or ovarian cancer will carry a mutation in either BRCA 1 or BRCA 2.

Women of reproductive age who carry these mutations are often counseled for risk reducing surgery including mastectomy and bilateral salpingo-oophorectomy (BSO) to prevent occurrence of cancer. BSO is typically recommended prior to the age at which the youngest family member was diagnosed with cancer, but ideally after child-bearing is complete.

1.18 Fertility preservation in hereditary breast cancer

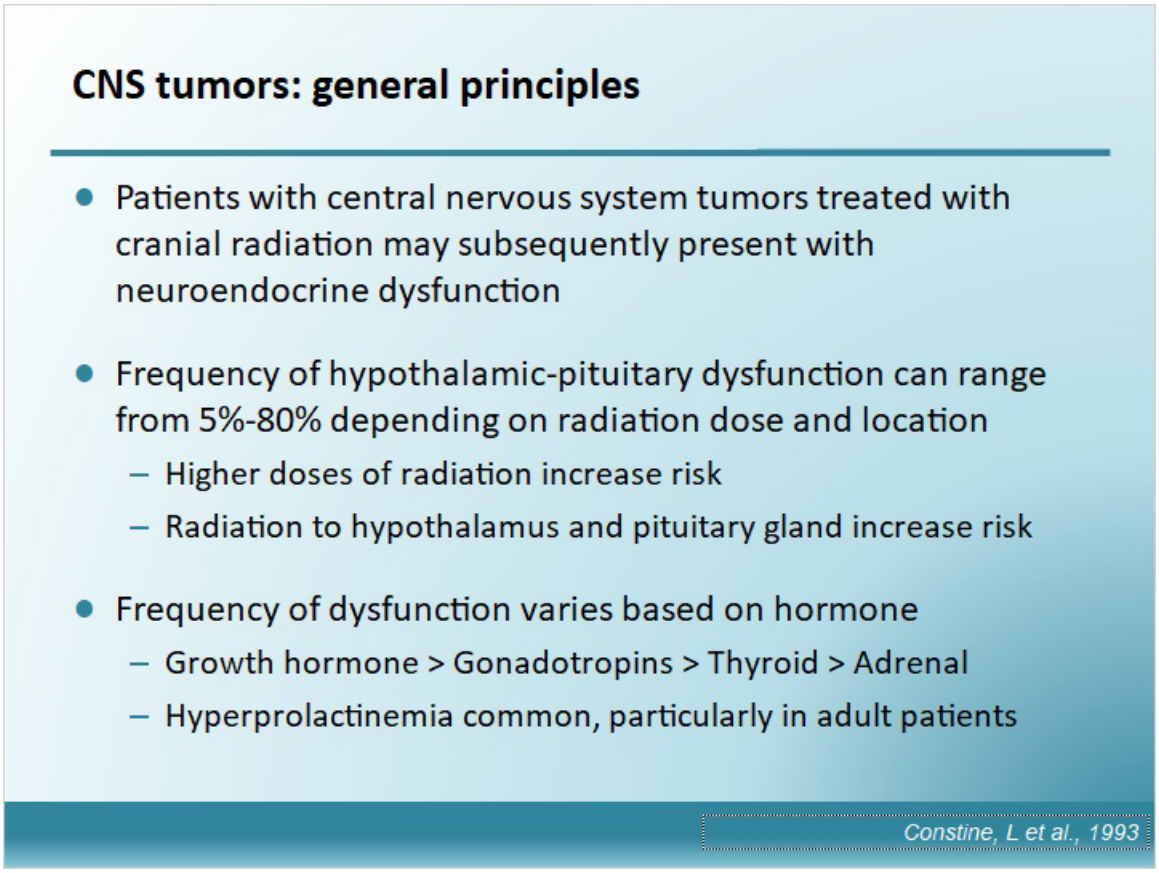


Notes:

In circumstances where BSO cannot be delayed, fertility preservation is an option. Embryo or oocyte cryopreservation is the best option depending upon the availability of partner sperm and/or a patient's willingness to use donor sperm. Ovarian tissue freezing is not recommended given potential risk of ovarian cancer with autologous transplanted tissue. Since patients typically do not have a firm time constraint prior to risk-reducing BSO, multiple IVF cycles could be attempted to increase the total number of cryopreserved gametes.

If a patient carries a BRCA mutation, pre-implantation genetic diagnosis should be offered as a means to screen embryos for the affected gene. PGD can be done at the time of fertility preservation or at the time when embryos will be utilized for pregnancy. Genetic counseling is appropriate in this population and should be recommended at the time of the fertility preservation consult.

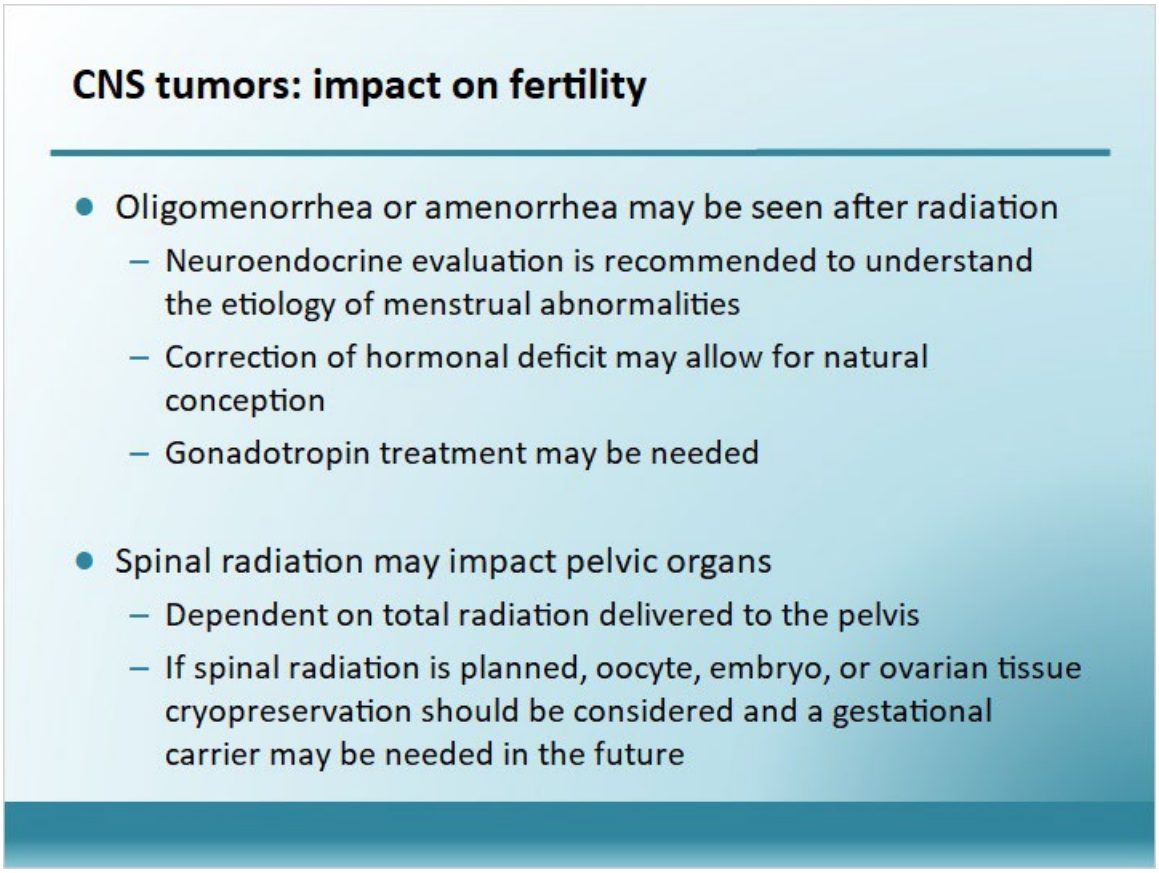
1.19 CNS tumors: general principles



Notes:

Central nervous system (CNS) tumors can be treated with surgery, chemotherapy, and/or radiation. Cranial radiation can lead to neuroendocrine dysfunction by impacting hypothalamic or pituitary function. The frequency of neuroendocrine dysfunction can range from 5 to 80 percent depending on the dose of radiation and the radiation field. Pituitary hormones differ in their sensitivity to radiation-induced damage. Reduced growth hormone levels are commonly associated with cranial radiation. Abnormal gonadotropin levels can occur in approximately 20 percent of patients receiving cranial radiation, while thyroid and adrenal abnormalities are rare, occurring in only approximately 5% of patients. Prolactin elevation is also commonly seen in post-cranial radiation, and is more common in adults than children.

1.20 CNS tumors: impact on fertility

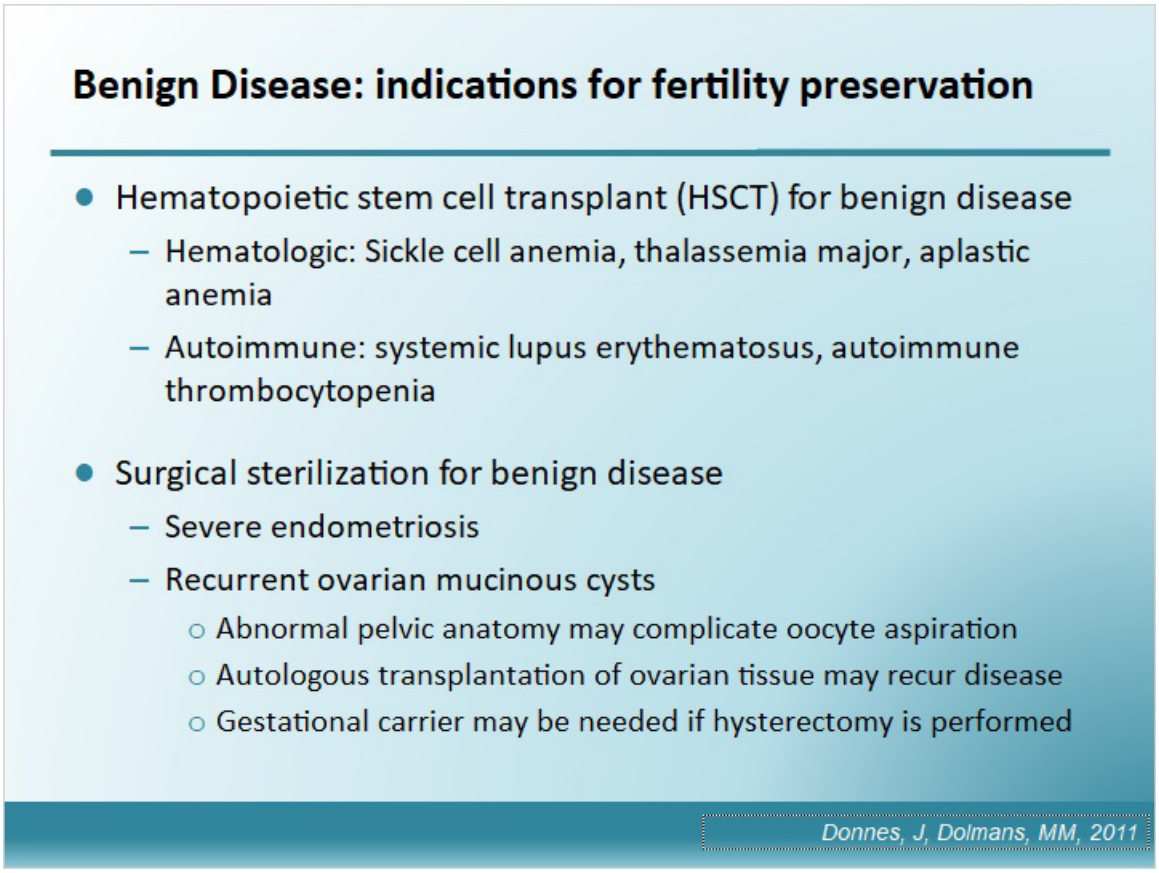


Notes:

Neuroendocrine dysfunction as a result of CNS radiation commonly presents as oligomenorrhea or amenorrhea in a woman of reproductive age. Hormonal evaluation is recommended, including dynamic testing to identify whether the deficiency is of hypothalamic or pituitary etiology. Correction of the underlying hormonal deficit may lead to resumption of normal menstrual cyclicity and allow for spontaneous conception. In patients with gonadotropin dysfunction, however, replacement with human menopausal gonadotropin may be necessary to restore fertility.

A second consideration in CNS tumors is the need for spinal radiation. Irradiation of CNS tumors can involve the spine at the level of the reproductive organs and damage both the ovaries and the uterus, necessitating a gestational carrier in the future. Understanding the planned radiation field and total radiation dosage can help plan for pre-treatment fertility preservation techniques if warranted.

1.21 Benign Disease: indications for fertility preservation

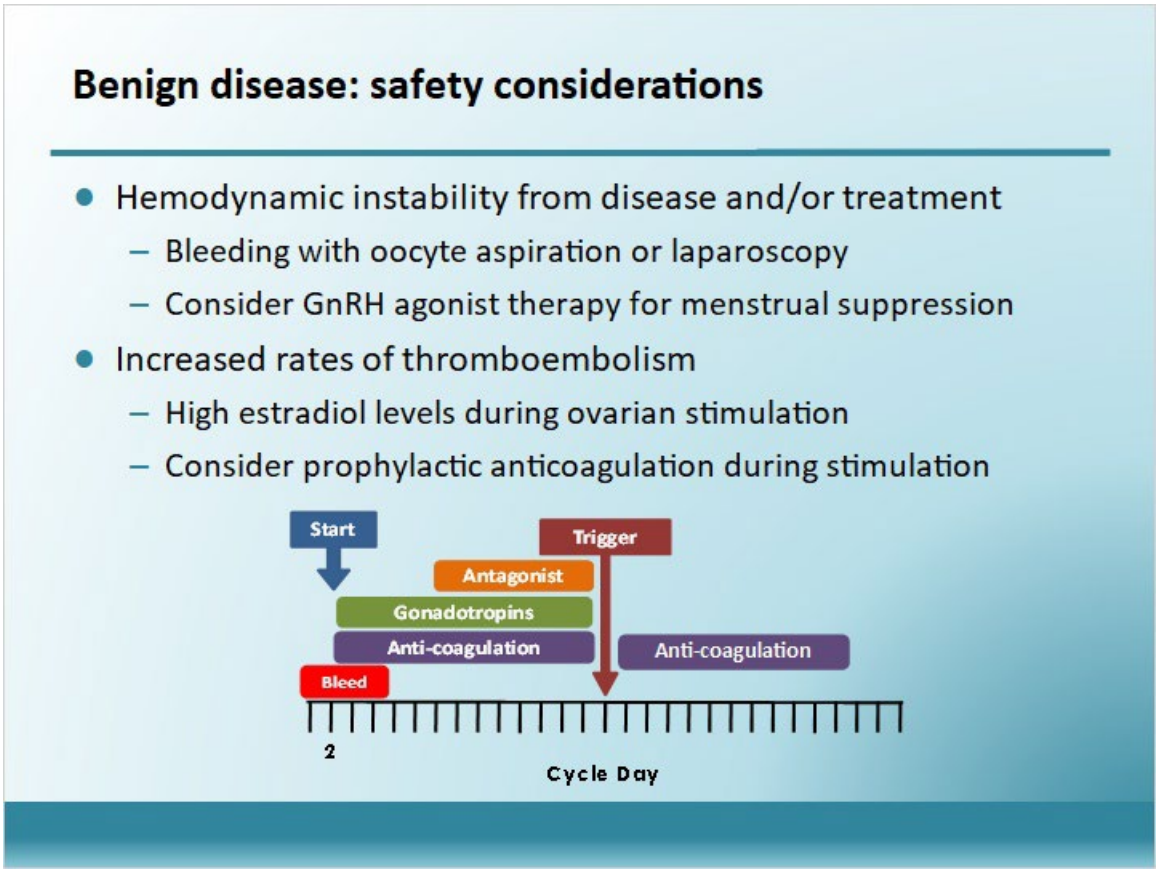


Notes:

Patients may also present to discuss fertility preservation prior to treatment for certain benign conditions. Hematopoietic stem cell transplant (HSCT) has been increasingly used for treatment of hematologic disease (including sickle cell anemia, thalassemia major, and aplastic anemia) and autoimmune diseases (such as systemic lupus erythematosus and autoimmune thrombocytopenia) unresponsive to immunosuppressant agents.

Patients undergoing surgical sterilization in cases of severe endometriosis or recurrent ovarian mucinous cysts refractory to medical therapy may also be candidates for fertility preservation, though the process can be complicated by the disease itself. Abnormal pelvic anatomy may complicate oocyte aspiration in patients undergoing embryo or oocyte banking. In cases of ovarian tissue cryopreservation, autologous transplantation may increase risk of disease recurrence. These issues should be discussed with the patient at the initial consultation, along with the possibility of a gestational carrier if hysterectomy is planned.

1.22 Benign disease: safety considerations

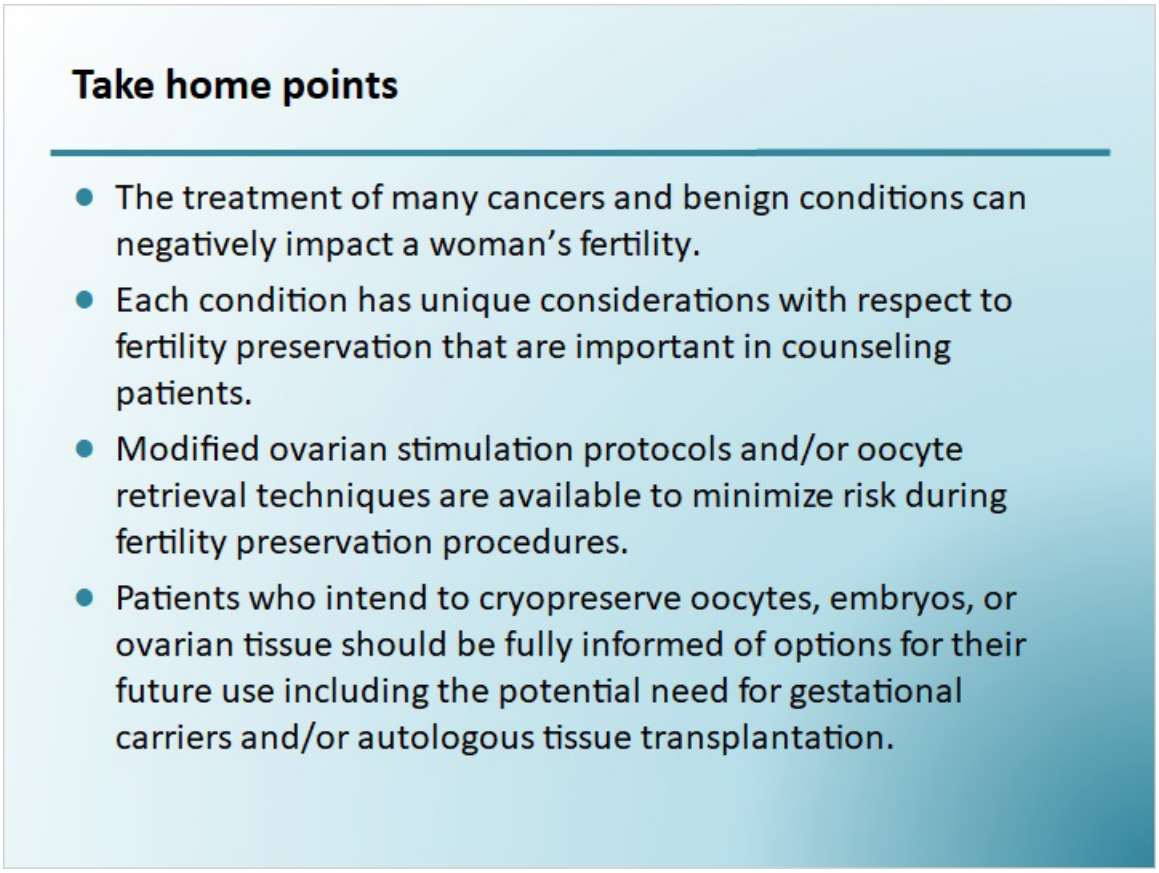


Notes:

Patients undergoing HSCT for hematologic or autoimmune diseases may face the same safety concerns as cancer patients including severe anemia and thrombocytopenia. Hemodynamic instability can complicate minor surgical procedures involved in fertility preservation. GnRH agonists for menstrual suppression should be considered in this population.

Certain benign diseases such as systemic lupus erythematosus put patients at a higher risk of venothromoembolic disease. The baseline risk can be further magnified by the high estradiol levels encountered during ovarian stimulation. Prophylactic anticoagulation should be considered during stimulation to decrease this risk. Typically, daily subcutaneous low-molecular weight heparin can be started with gonadotropin stimulation, discontinued the morning of hCG trigger, and restarted within 12-24 hours of transvaginal oocyte aspiration.

1.23 Take home points



Notes:

In summary, many cancers and benign conditions or their treatment can negatively impact a woman's fertility, and each condition has unique considerations with respect to safety and efficacy of fertility preservation that are important to include in patient counseling. Modified protocols can be used to minimize risk during ovarian stimulation or oocyte retrieval. An important part of any fertility preservation consultation is discussing future use of cryopreserved gametes or ovarian tissue, including the potential need for gestational carriers or autologous transplantation of tissue.

1.24 Thank you!

Notes:

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