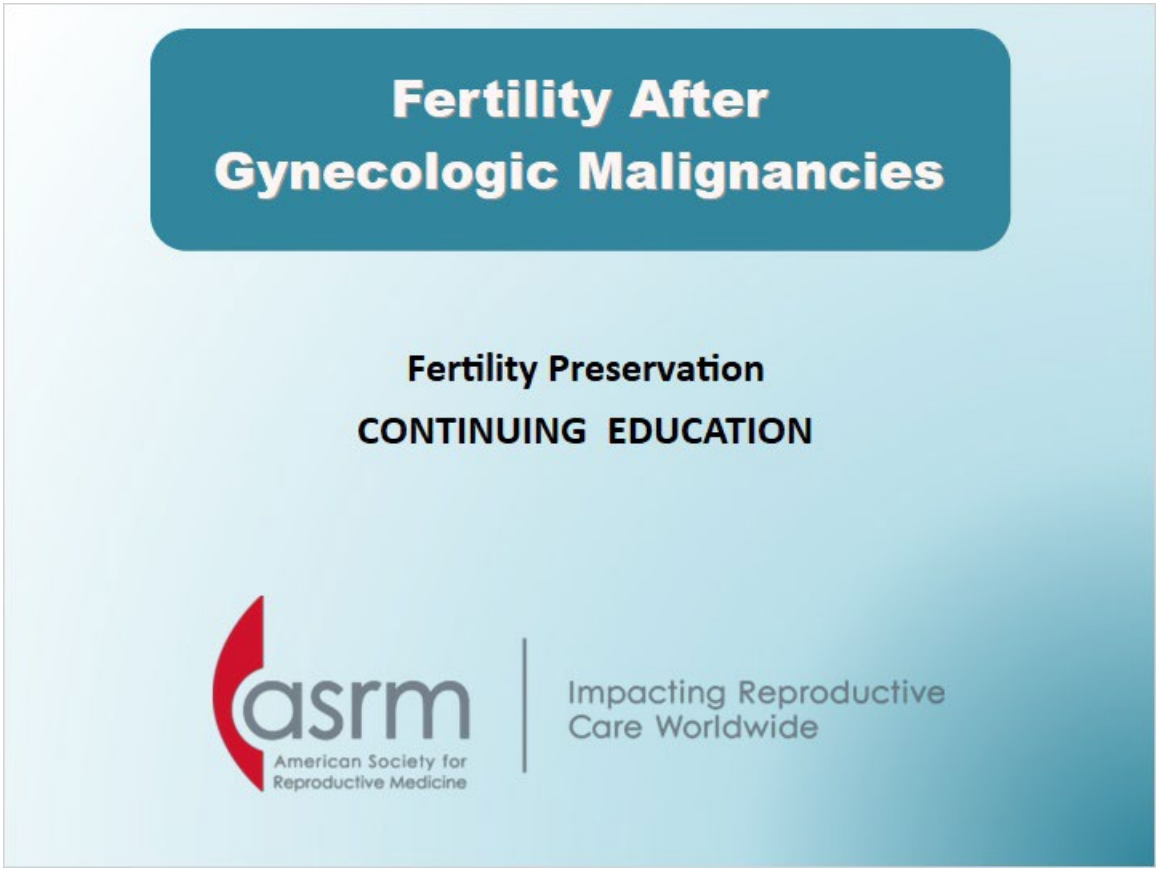
MD120 Lesson 6

1. MD120_L6

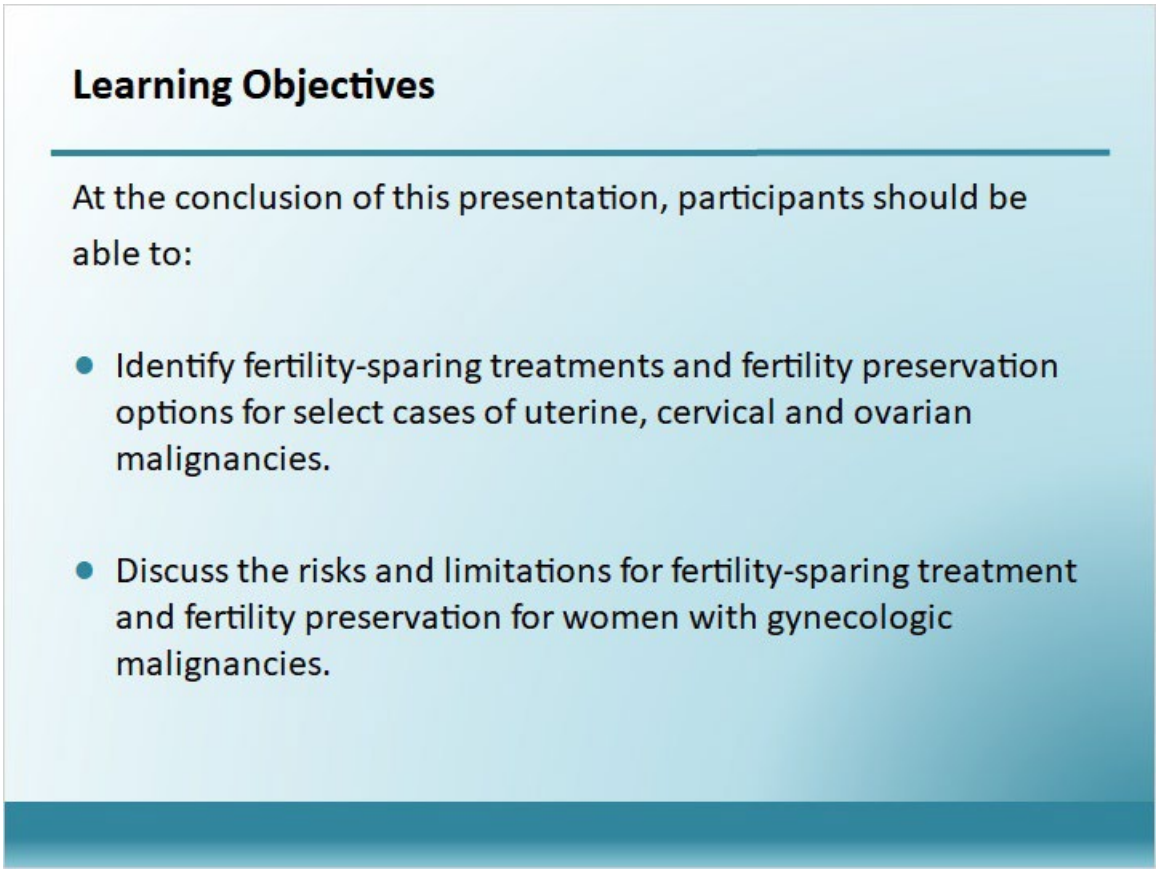
1.1 Fertility After



Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Fertility after Gynecologic Malignancies."

1.2 Learning Objectives

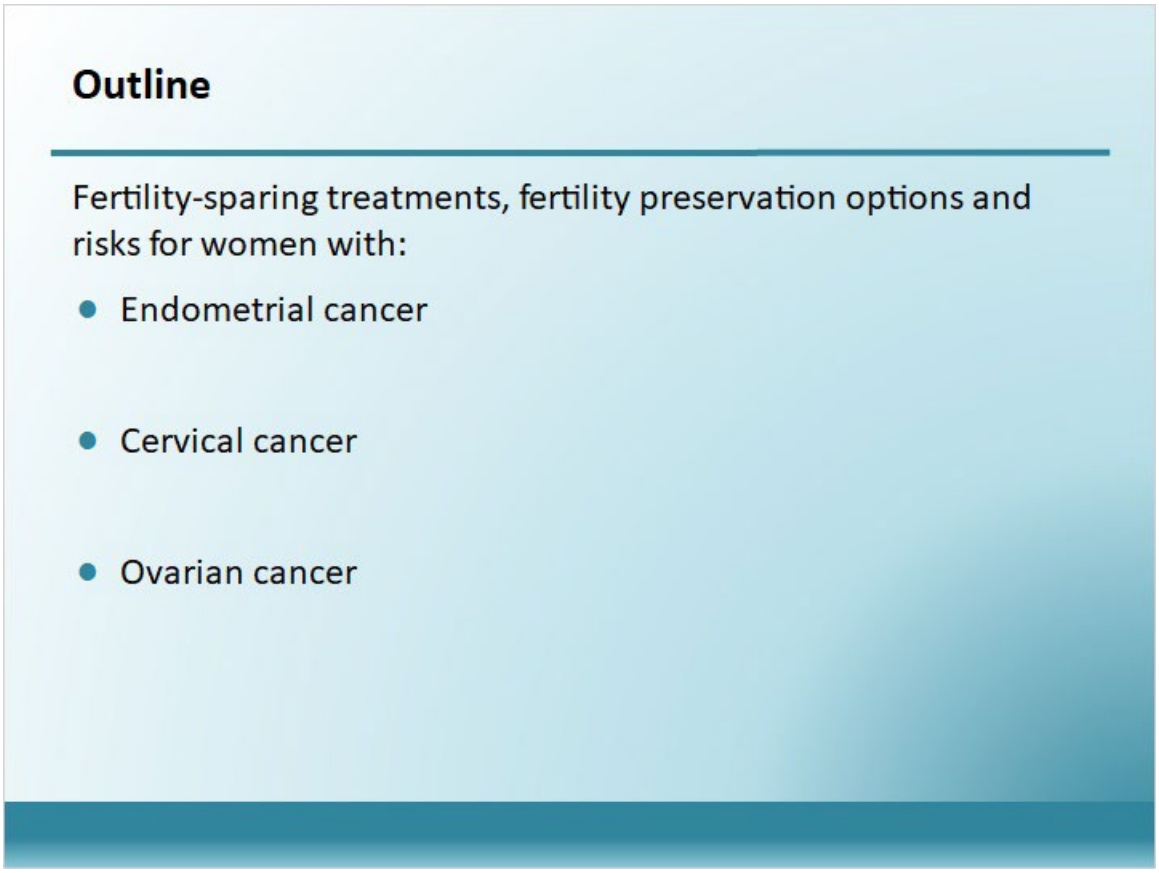


Notes:

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

1. Identify fertility-sparing treatment and fertility preservation options for select cases of uterine, cervical, and ovarian malignancies
2. Discuss the risks and limitations for fertility-sparing treatment and fertility preservation for women with gynecologic malignancies

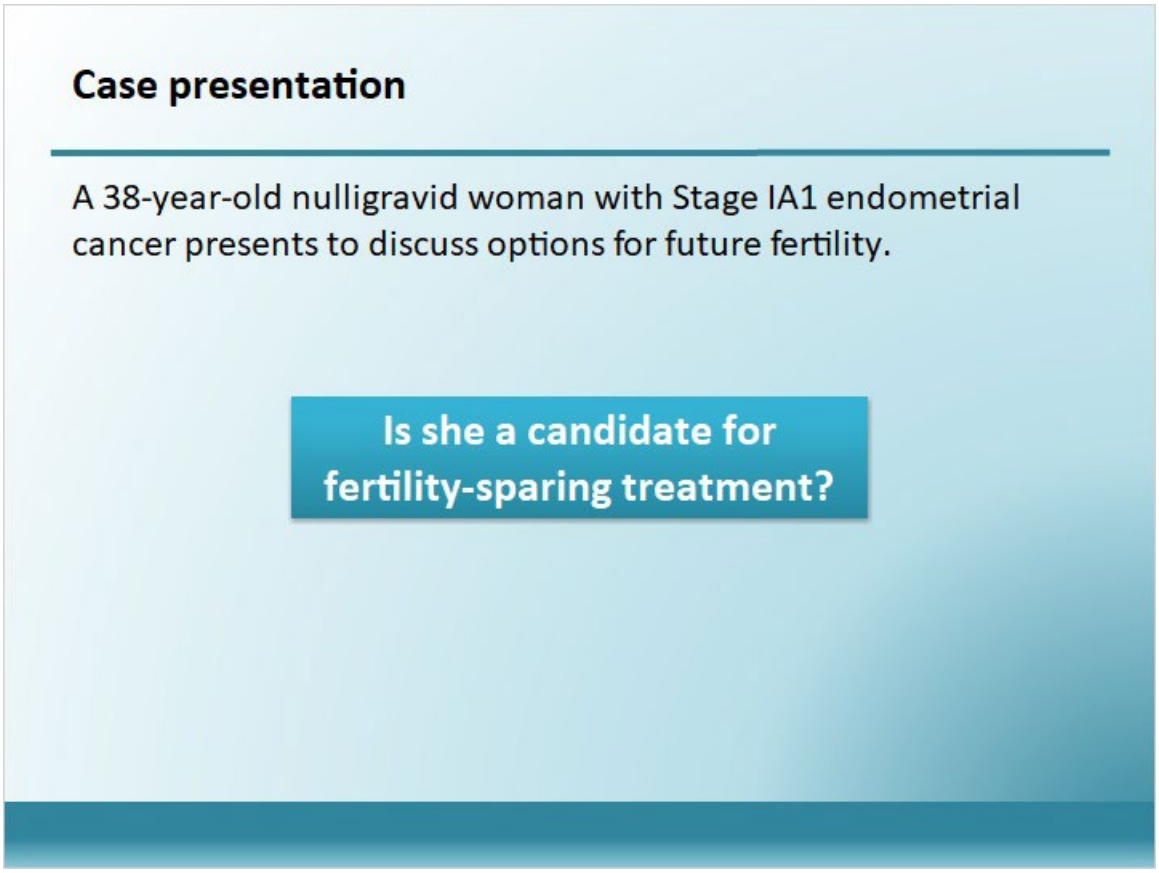
1.3 Outline



Notes:

This presentation will outline the unique challenges of fertility-sparing, fertility preservation options and associated risks for women with endometrial cancer, cervical cancer, and ovarian cancer.

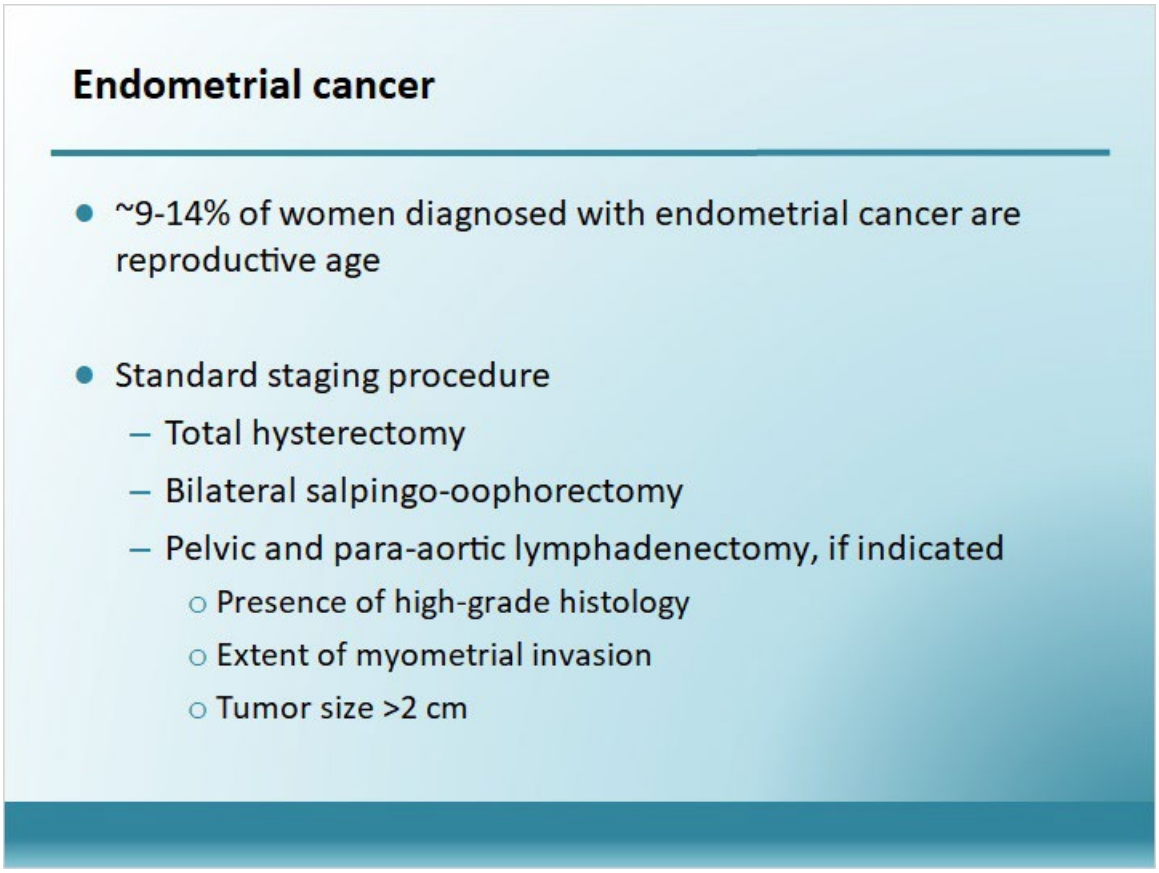
1.4 Case presentation



Notes:

The discussion of options for women with endometrial cancer will begin with a case presentation. This is a 38-year-old nulligravid women with Stage IA, grade 1, endometrial cancer based on dilation and curettage sampling. She is interested in future fertility. What are her options for fertility-sparing treatment for early-stage endometrial cancer?

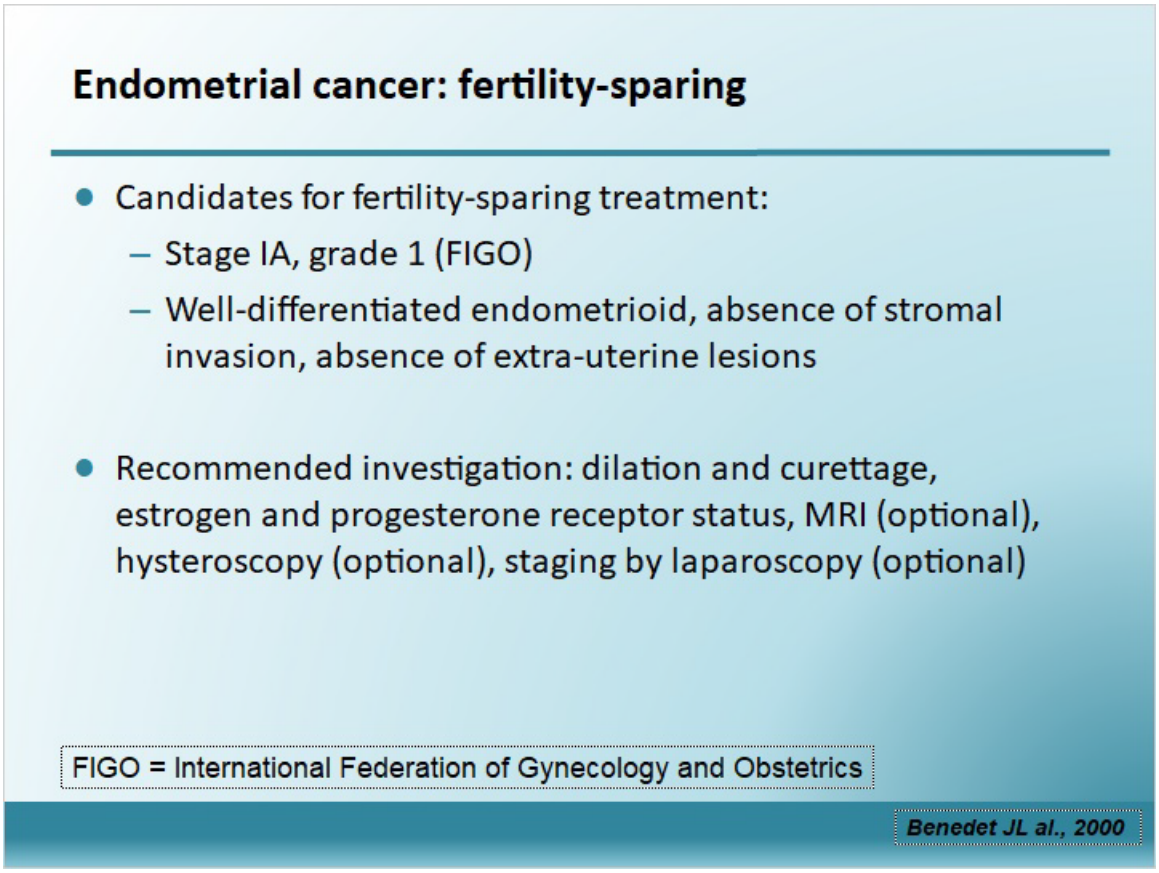
1.5 Endometrial cancer



Notes:

Endometrial cancer of the uterus is the most common gynecologic malignancy in the developed world and 9%-14% of women who are diagnosed are of reproductive age. The standard staging procedure for endometrial cancer is a total hysterectomy with bilateral salpingo-oophorectomy. Pelvic- and para-aortic lymphadenectomy is performed selectively depending upon the presence of high-grade histology, extent of myometrial invasion, and tumor size >2 cm.

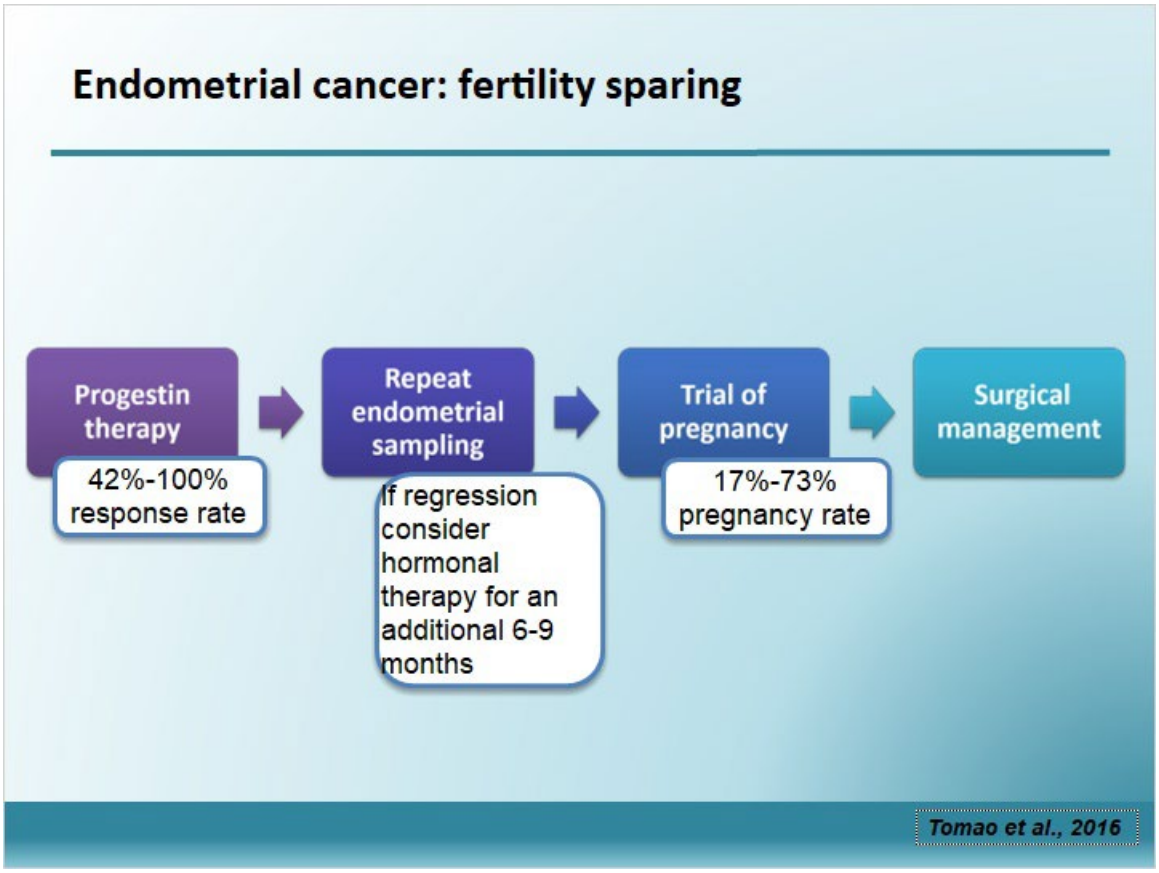
1.6 Endometrial cancer: fertility-sparing



Notes:

Women with endometrial cancer who have well-differentiated lesions with the absence of stromal invasion and extra-uterine lesions may consider fertility-sparing treatment. In lieu of surgical staging, these patients should be evaluated for high-grade or advanced-stage disease through dilation and curettage and imaging including MRI. The grade of the carcinoma can be obtained from the D&C sample and myometrial invasion can be assessed through MRI. In addition, transvaginal ultrasound or MRI can be used to assess for adnexal masses. Additional surgical evaluation with laparoscopy to exclude extrauterine spread should be individualized.

1.7 Endometrial cancer: fertility sparing



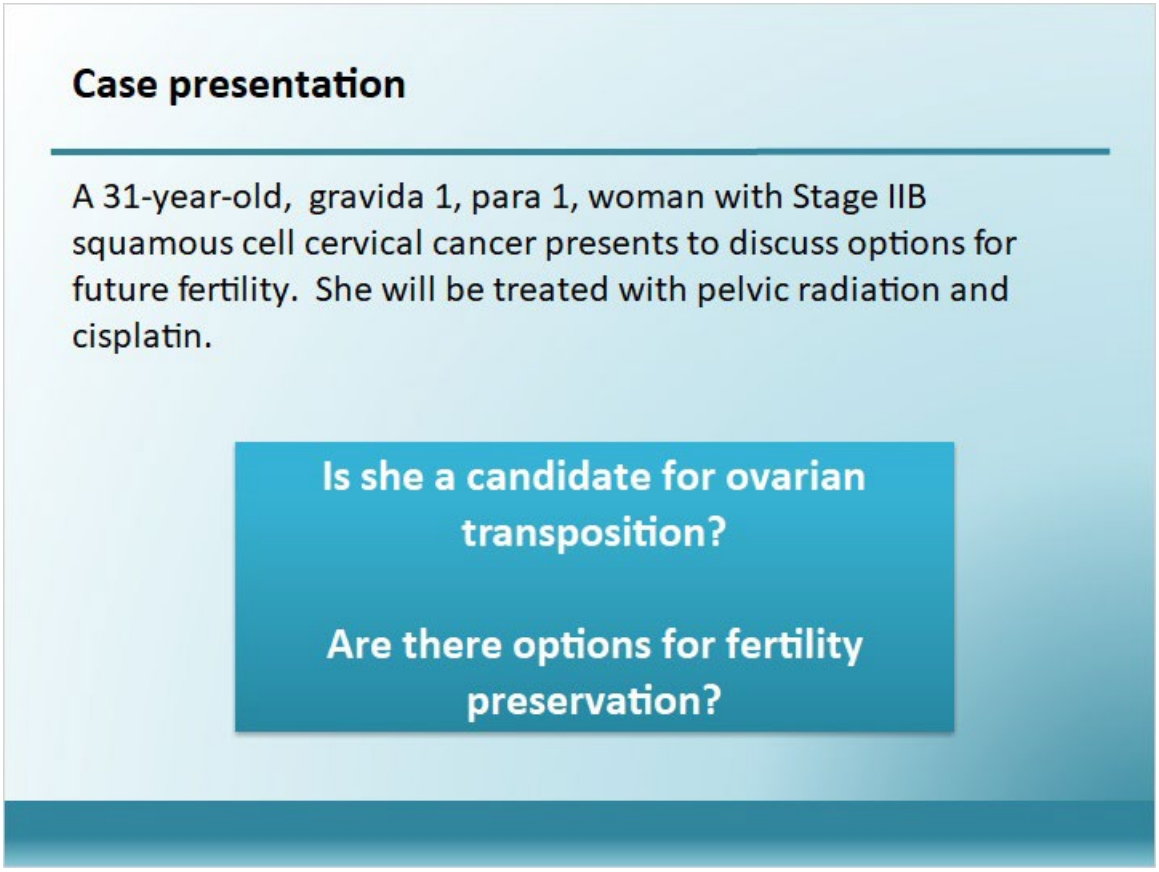
Notes:

In appropriately screened candidates with early-stage endometrial cancer that is confined to the uterus, a trial of progestin therapy, such as megestrol acetate 160 mg daily, medroxyprogesterone acetate at 500-600 mg daily and/or the levonorgestrel intrauterine device (IUD), can be initiated. Repeat endometrial sampling is performed in 3 months to determine whether there is disease regression, persistence, or progression.

In a recent review, 42-100% of women treated with a progestin demonstrated a response. The time to complete response varied from 1 to 18 months with a median of 6 months. If persistent disease without any improvement in cellular architecture or disease progression is identified after 6-9 months of progestin therapy, the recommendation is to proceed with hysterectomy. In cases where regression occurs, continued hormonal therapy for an additional 6-9 months may be considered. At the completion of medical management, the patient is encouraged to pursue pregnancy with follow-up surveillance for disease recurrence. The live-birth rate for women with a history of endometrial cancer has been reported to be as high as 73% with the use of fertility medications. As endometrial cancer is linked to obesity, polycystic ovary syndrome, and anovulation, many women with this diagnosis may have primary or

secondary infertility, and may require assisted reproductive technologies. The use of fertility medications in this population does not appear to worsen their prognosis. After delivery, routine cancer surveillance is advised as 20%-40% will experience a recurrence and definitive surgical management with hysterectomy may be recommended after the completion of childbearing.

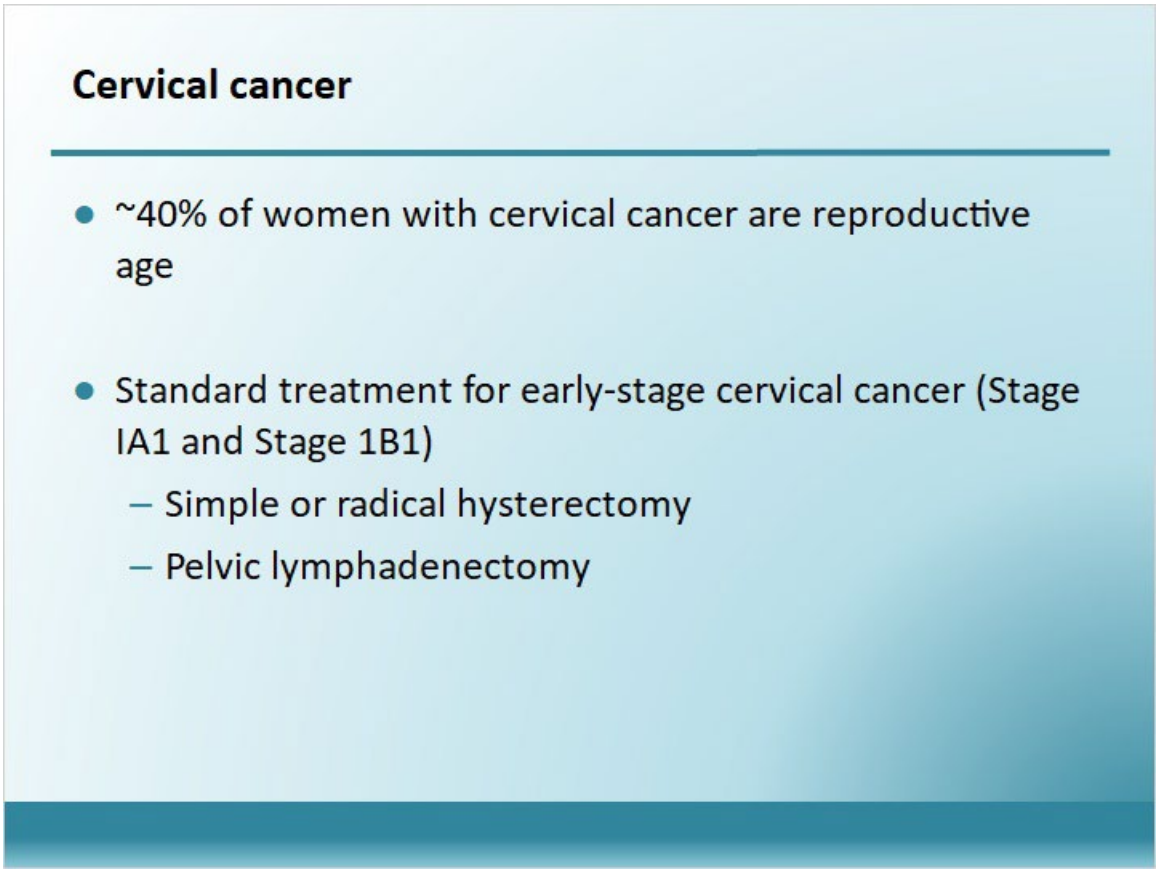
1.8 Case presentation



Notes:

Next, we will review the options for fertility-sparing treatment and preservation for women with cervical cancer. This is a case of a 31-year-old gravida 1, para 1 woman with Stage IIB squamous cell cervical cancer who will be treated with pelvic radiation and cisplatin. She is interested in future fertility. Is she a candidate for ovarian transposition? Are there safe and effective fertility preservation options for women with cervical cancer?

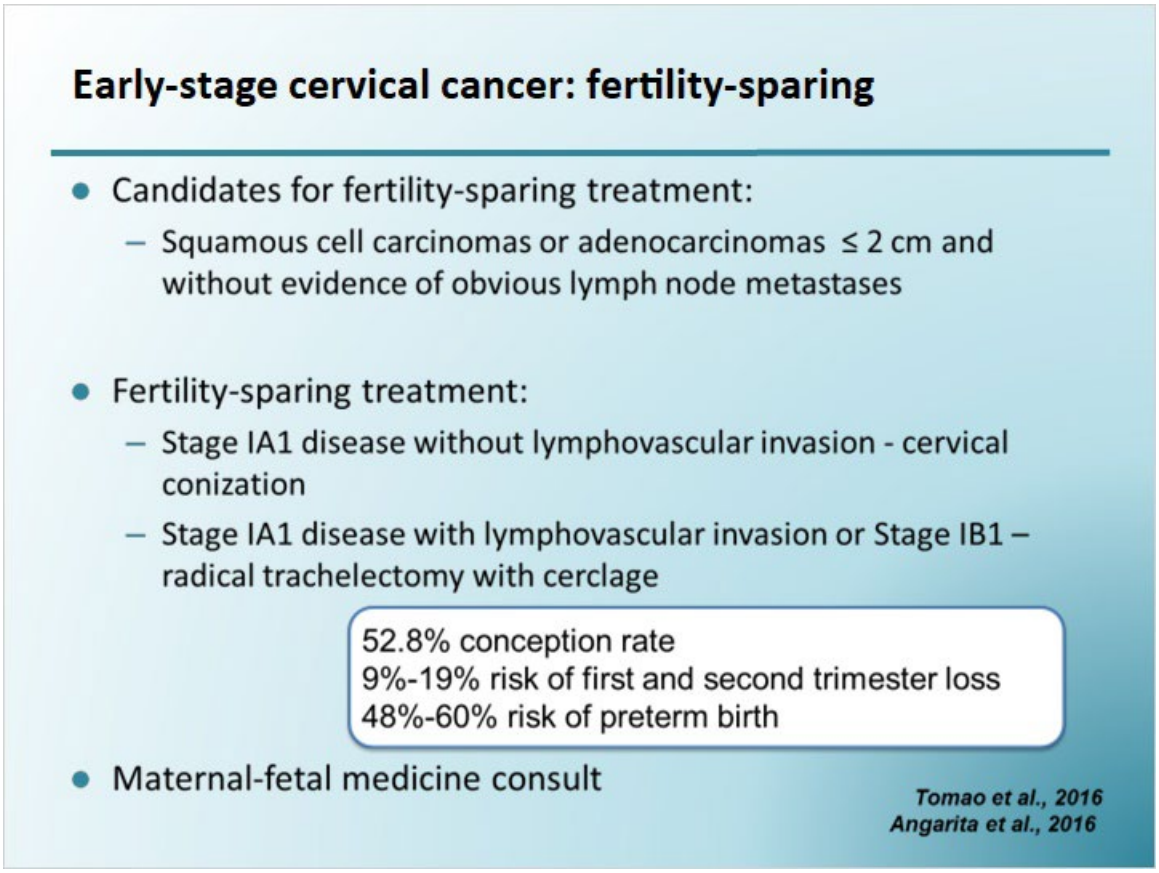
1.9 Cervical cancer



Notes:

Cervical cancer is the most common gynecologic malignancy worldwide and is more likely to affect women of reproductive age than other gynecologic malignancies with 40% of all new cases diagnosed in women under the age of 40 years. One of the standard treatment options for women with early-stage cervical cancer is a simple or radical hysterectomy with pelvic lymphadenectomy.

1.10 Early-stage cervical cancer: fertility-sparing

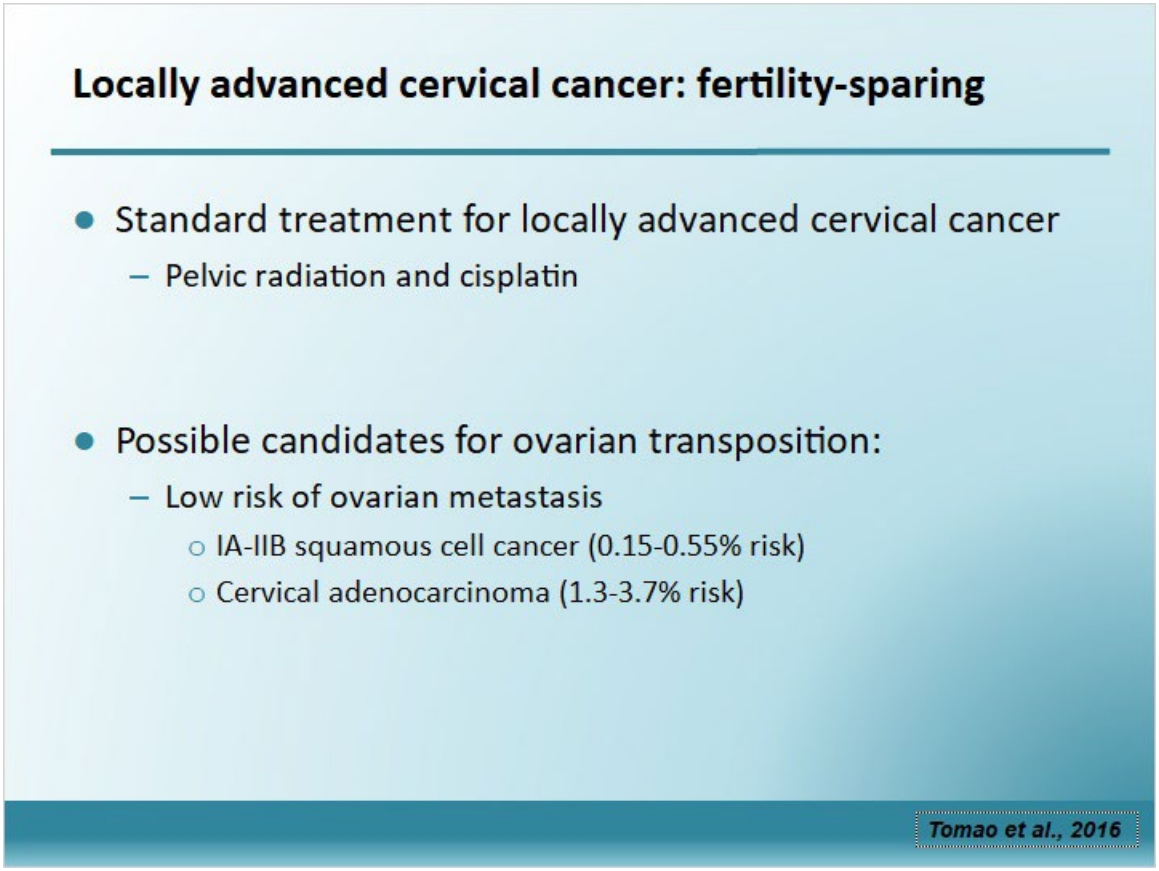


Notes:

Women with local early-stage squamous cell carcinoma or squamous cell carcinomas of the cervix, defined as tumors ≤2 cm and without evidence of lymph node metastases can opt to undergo cervical conization or radical trachelectomy if they wish to pursue pregnancy in the future. A study of women 40 years or younger with stage IA1 disease using the Surveillance, Epidemiology, and End Results (SEER) database found no significant difference in 5-year survival between cervical conization and radical hysterectomy.

If lymphovascular space invasion is present in the setting of Stage IA1 or if Stage IB1 disease, radical trachelectomy is recommended for women who wish to pursue pregnancy in the future. A cerclage can be placed at the time of the trachelectomy. After radical trachelectomy, a 52.8% 5-year cumulative conception rate has been reported. The risks of first and second trimester losses range from 9.5-19% and a 48-60% risk of preterm birth has been reported. Given the high risk for preterm birth, transabdominal cerclage may be recommended and consultation with a maternal-fetal medicine specialist should be considered before attempting pregnancy.

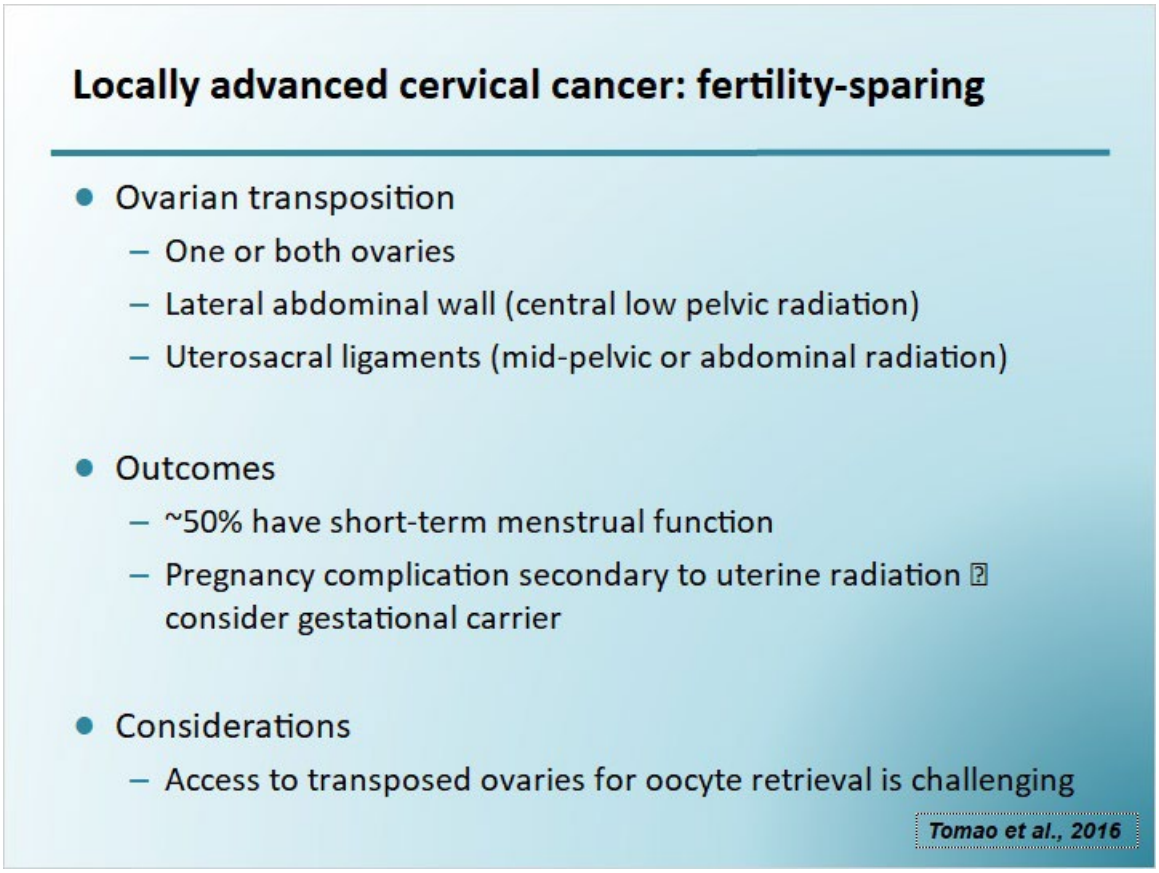
1.11 Locally advanced cervical cancer: fertility-sparing



Notes:

Women with locally advanced cervical cancer or high risk features after hysterectomy may be faced with pelvic radiation and cisplatin for chemosensitization. Ovarian transposition can be performed prior to pelvic radiation to move the ovary or ovaries out of the radiation field. Candidates for ovarian transposition should be evaluated for the risk of ovarian metastasis using preoperative MRI or PET imaging. For women with Stage IA-IIB squamous cell cancer, the risk of ovarian metastases is 0.15-0.55% whereas for women with adenocarcinoma of the cervix, the risk of metastases is 1.3%-3.7%.

1.12 Locally advanced cervical cancer: fertility-sparing



Notes:

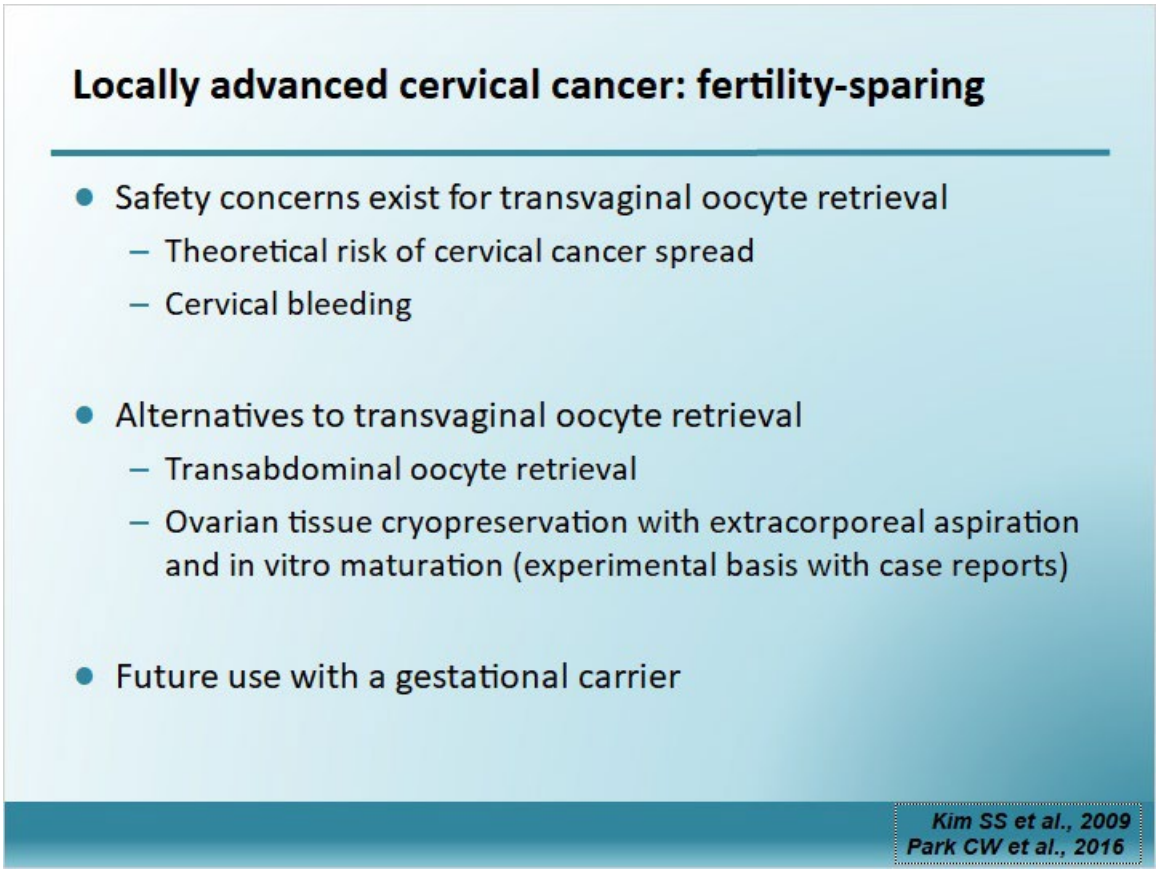
Ovarian transposition can be performed with one or both ovaries. The ovary can be transposed to the lateral abdominal wall along the ipsilateral paracolic gutter in the case of central low pelvic radiation, or with ligation to the uterosacral ligament in the case of midpelvic or abdominal radiation.

The goal of ovarian transposition is to spare ovarian function from the sterilizing impact of radiation. The overall success rate as judged by preservation of short-term menstrual function is approximately 50%, although there is a wide variation in the reported success rates ranging from 16% to 90%. The failure of this method to preserve ovarian function may be due to scatter radiation, compromise of the transposed ovary blood supply, patient age, radiation dose, whether the ovaries are shielded during the radiation procedure and whether concomitant chemotherapy is used.

While ovarian transposition may preserve menstrual function, there are limited data regarding future fertility. Given that pelvic radiation can alter the elasticity and vasculature of the uterus, there is an increased risk of implantation failure and pregnancy complications such as spontaneous miscarriage, preterm labor, and growth

restriction. Given the risks of pregnancy complications, a gestational carrier can be considered. There are case reports of successful IVF following transabdominal oocyte retrieval and embryo transfer to a gestational carrier resulting in birth in patients who received radiation after radical hysterectomy and ovarian transposition.

1.13 Locally advanced cervical cancer: fertility-sparing

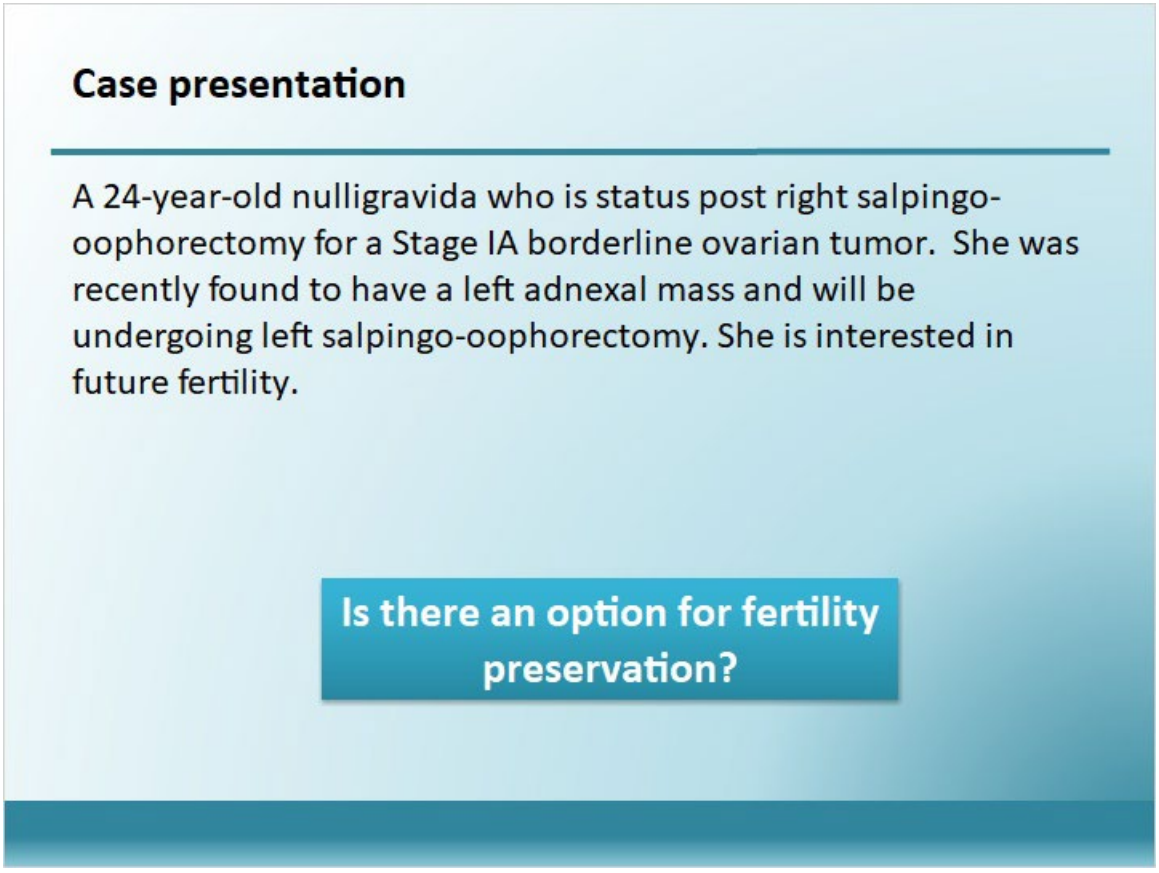


Notes:

There is no literature on the safety of oocyte or embryo banking prior to pelvic radiation and cisplatin. The concerns regarding the safety of oocyte or embryo banking prior to treatment for cervical cancer are related to transvaginal oocyte retrieval. Transvaginal oocyte retrieval could theoretically increase the risk of spreading the cervical cancer or induce cervical bleeding. In select candidates with minimal parametrial or vaginal involvement, transvaginal oocyte retrieval could be done with appropriate counseling regarding the lack of literature regarding safety. Alternatively, a transabdominal oocyte retrieval could be performed. Another alternative includes ovarian tissue cryopreservation at the time of transposition, though autotransplantation with this diagnosis has not been performed. At the time of ovarian tissue cryopreservation,

mature oocytes may be aspirated and cryopreserved or fertilized for embryo banking. In addition, immature oocytes may be matured in vitro and banked, though in vitro maturation is performed in a small number of ART labs in the United States. In the event that oocytes or embryos have been banked, future use would likely require a gestational carrier. While uterine transplantation has recently been described, this advance will likely not be an option for women with advanced cervical cancer considering the increased risk of radiation-induced vascular changes.

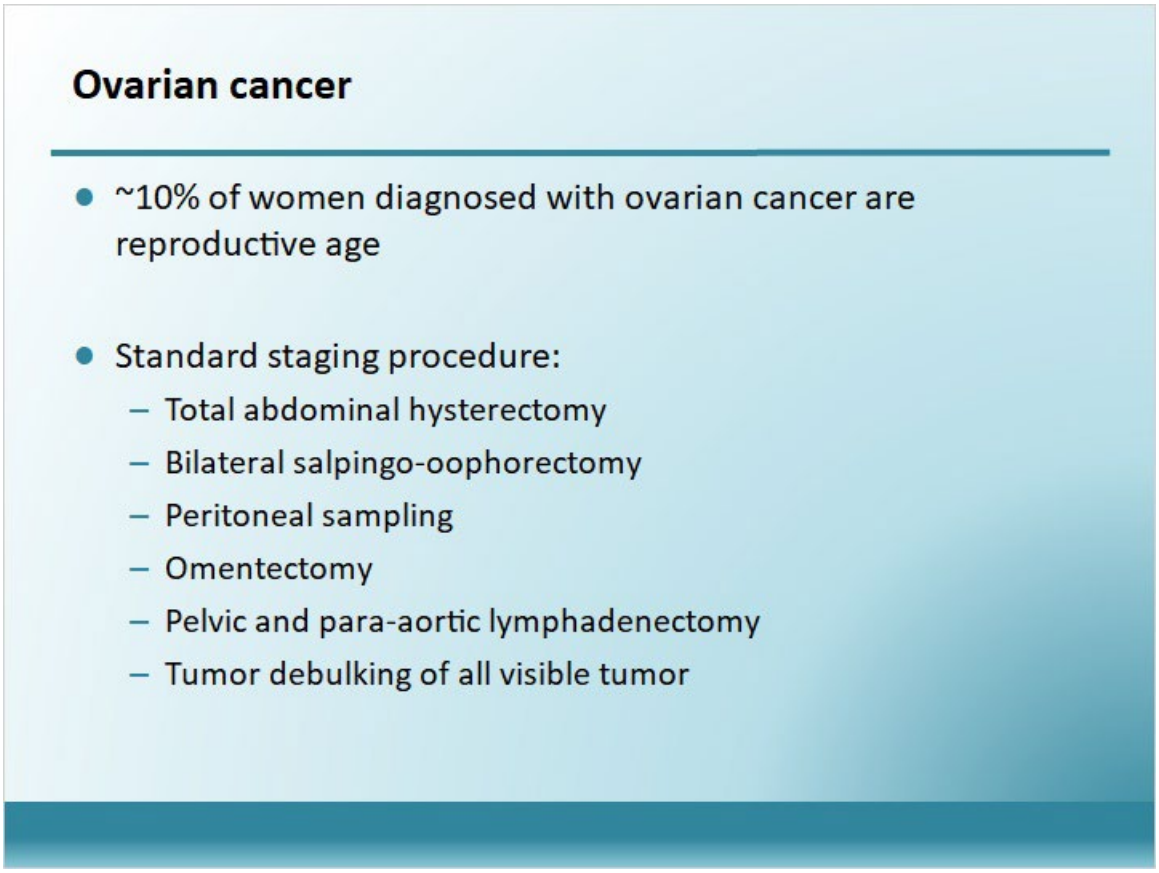
1.14 Case presentation



Notes:

The final case will illustrate the options for fertility-sparing treatment and fertility preservation options for women with ovarian cancer. This is a 24-year-old nulligravida who is status post a right salpingo-oophorectomy for a Stage IA borderline ovarian tumor. She was recently found to have a left adnexal mass and will be undergoing left salpingo-oophorectomy. She is interested in future fertility.

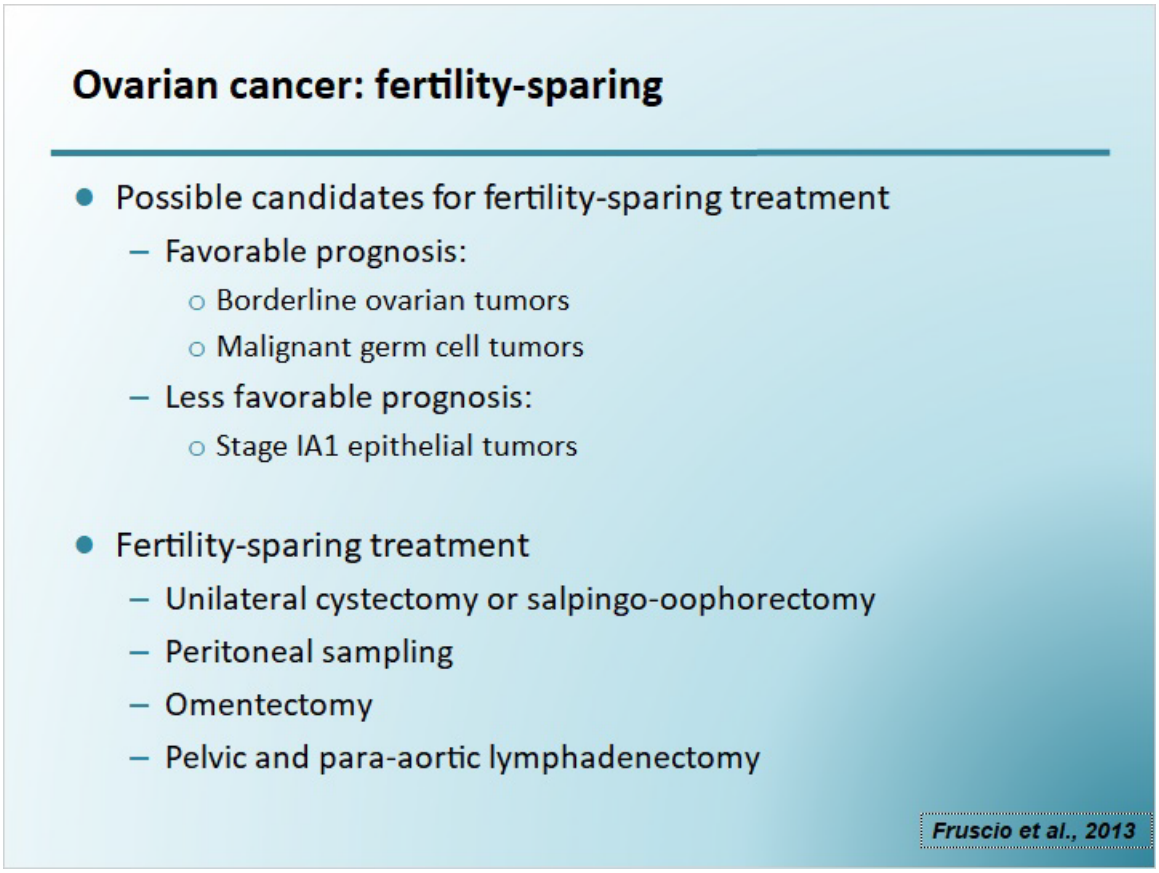
1.15 Ovarian cancer



Notes:

Ovarian cancer is uncommon among women of reproductive age. Approximately 10% of ovarian cancer cases are diagnosed in women under the age of 40 years. The standard staging procedure and surgical treatment for ovarian cancer is total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal samplings, omentectomy, pelvic and para-aortic lymph node dissection and tumor debulking of all visible tumor.

1.16 Ovarian cancer: fertility-sparing



Notes:

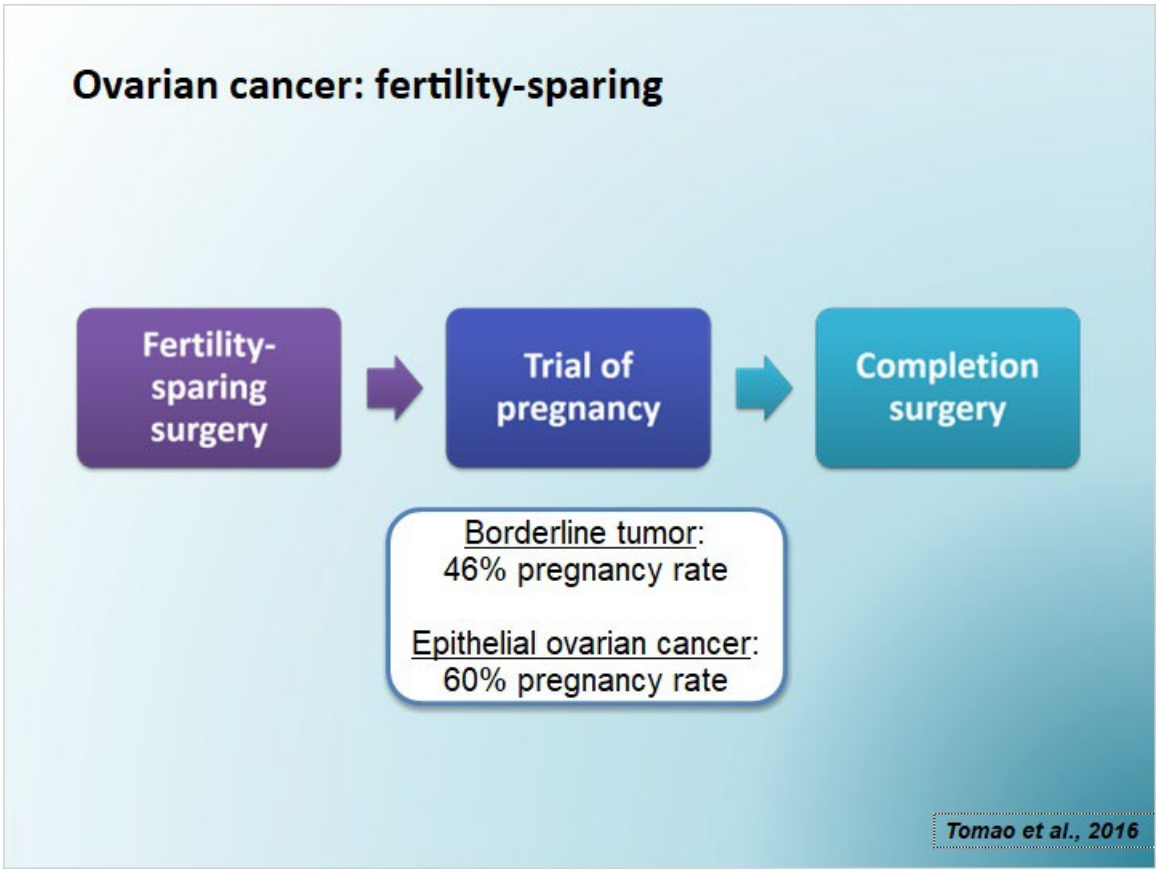
Women with select cases of ovarian tumors may be candidates for fertility-sparing treatment. Borderline tumors of the ovary are characterized by a lack of stromal invasion as well as serous, mucinous, or endometrioid histology. Borderline ovarian tumors are generally encountered in women 10-15 years younger than women with epithelial ovarian cancer. These patients have a relatively favorable prognosis compared with the prognosis for epithelial ovarian cancer making fertility-sparing surgery an option for women with borderline ovarian cancers. Relapse is higher with fertility-sparing treatment, though mortality does not appear to be increased.

For women with malignant ovarian germ cell tumors fertility-sparing surgery is the standard treatment as this diagnosis carries a favorable prognosis. Chemotherapy may be avoided in early-stage disease and platinum-based therapies may achieve a cure in advanced stage disease with preservation of fertility.

There are limited data about the use of fertility-sparing surgery in women with early-stage epithelial ovarian cancer. In a large retrospective study of 240 women with epithelial ovarian cancer confined to the ovaries who underwent fertility-sparing

surgery, 11.3% of the women relapsed and 4.6% died of progressive disease after a median follow-up of 9 years. The authors proposed a conservative approach consisting of cystectomy or unilateral oophorectomy, omentectomy, pelvic washings, at least 8 peritoneal biopsies, endometrial biopsy, and evaluation of pelvic and para-aortic lymph nodes for appropriately selected young women with cancer. However, they recommended careful monitoring given the chance of relapse.

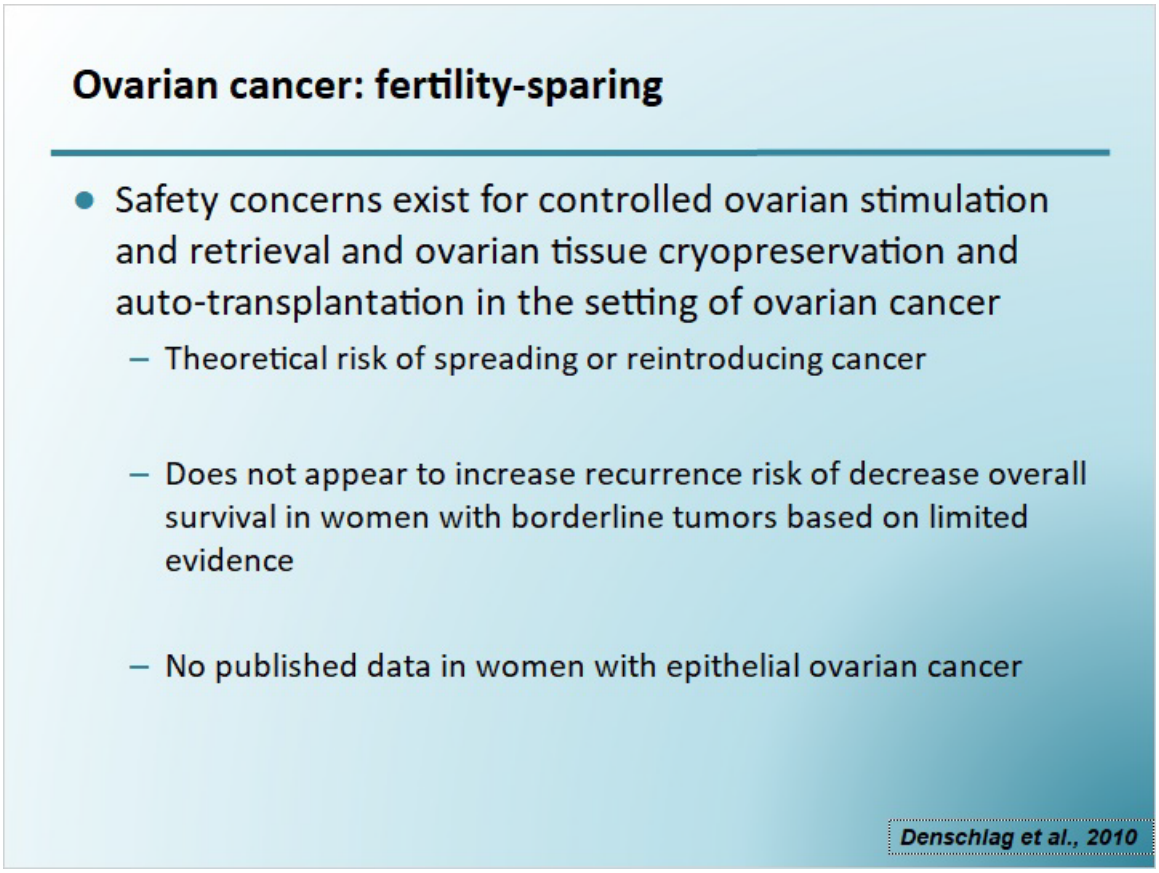
1.17 Ovarian cancer: fertility-sparing



Notes:

After fertility-sparing treatment for borderline tumors, malignant germ cell tumors and possibly early-stage epithelial ovarian cancer, patients desiring pregnancy should be counseled about the risk of diminished ovarian reserve and risk of tubal distortion after surgery. Most recurrences of borderline tumors will occur within the first 2 years this period of surveillance. Spontaneous pregnancy rates of 46% for borderline tumors and 60% for early-stage epithelial ovarian cancers have been reported after fertility-sparing treatment.

1.18 Ovarian cancer: fertility-sparing

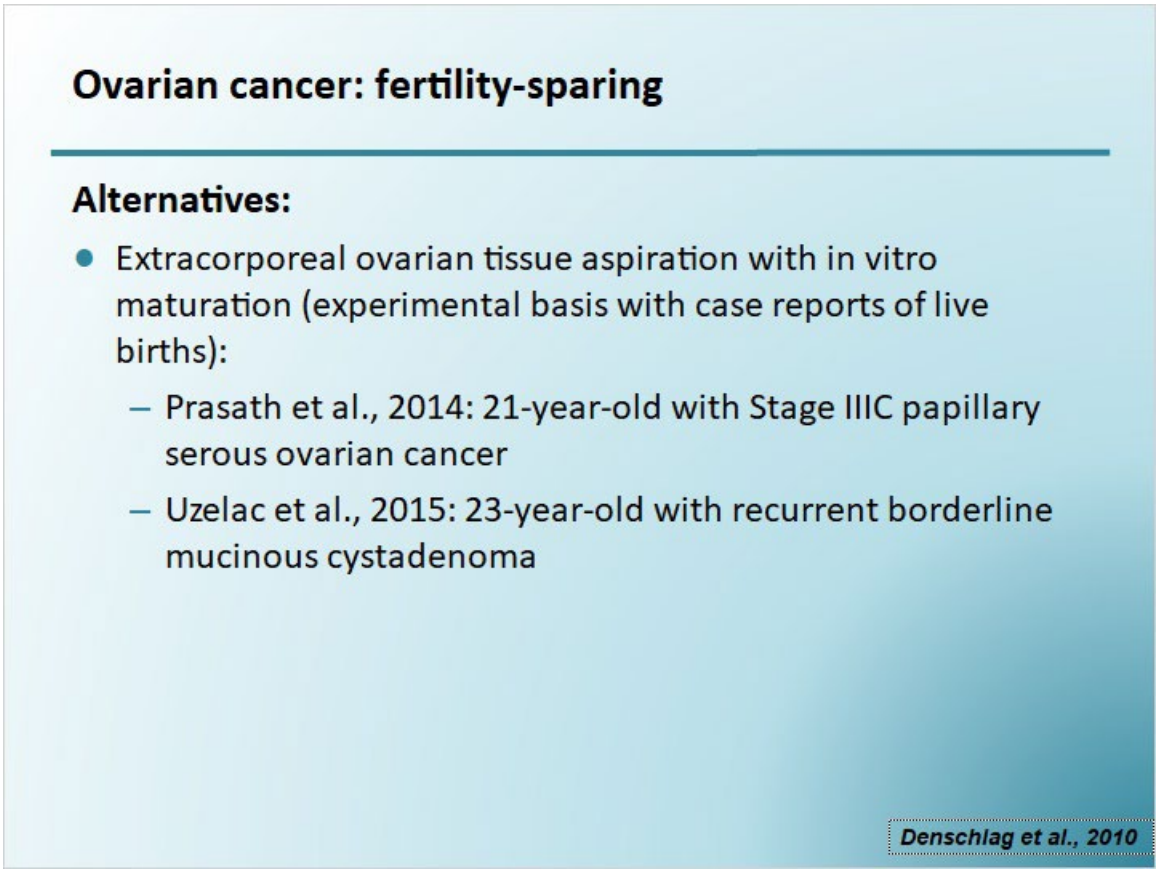


Notes:

In cases where infertility was previously diagnosed or the patient is not ready to conceive, oocyte and embryo banking after fertility-sparing surgery for borderline tumors has been described, although the safety of this approach is questionable. In a review of 62 patients who underwent oocyte or embryo banking after surgery for a borderline tumor, the live-birth rate was 28.3% per cycle. After a median follow-up of 52 months, 12/62 patients had a recurrence, but none died of disease. The recurrence risk in this population is similar to the recurrence risk in women who underwent fertility sparing surgery for borderline tumors but did not oocyte or embryo bank after surgery.

There are no published reports of fertility outcomes, recurrence risk and overall survival in women with early stage epithelial ovarian cancer who undergo oocyte and embryo banking after fertility-sparing surgery.

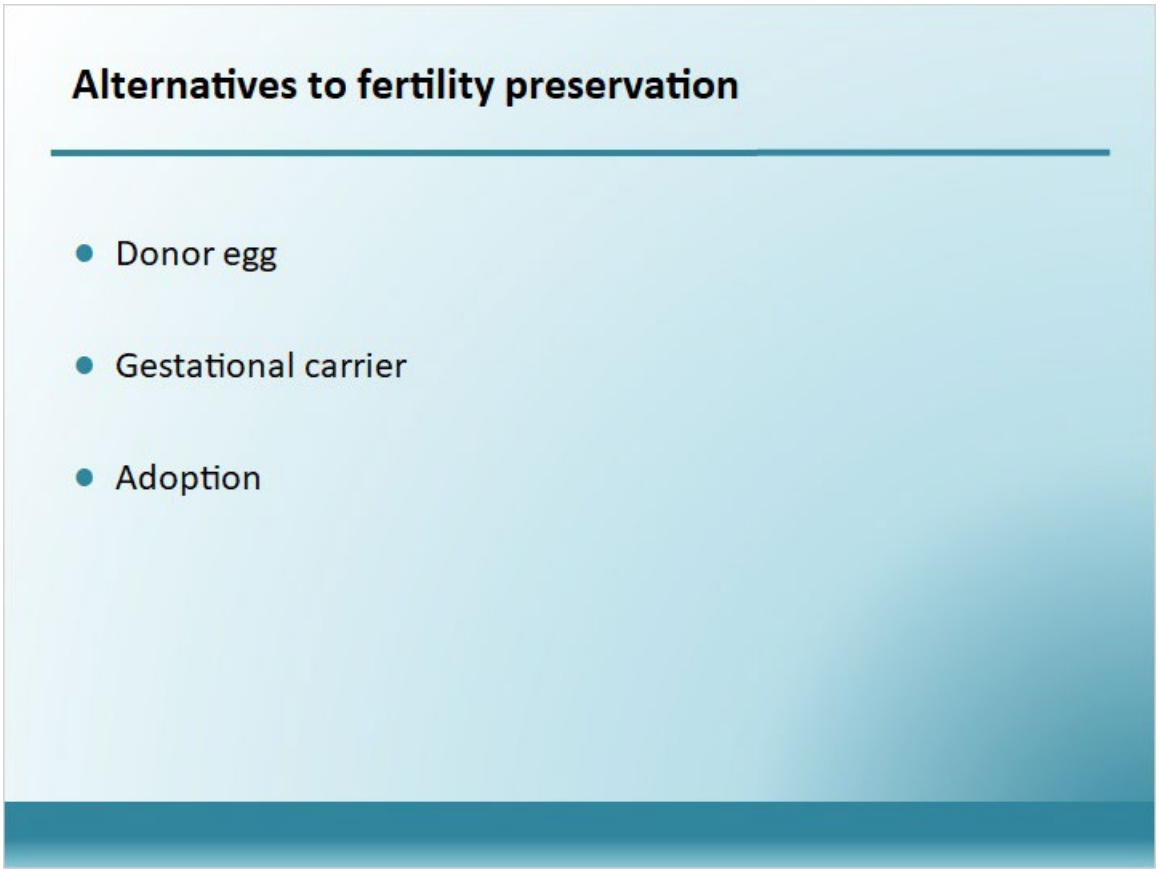
1.19 Ovarian cancer: fertility-sparing



Notes:

Given the concerns of advancing the progression of epithelial ovarian cancer with controlled ovarian stimulation and oocyte retrieval, and the risk of reintroducing ovarian cancer through ovarian tissue cryopreservation with autotransplantation, there have been case reports of extracorporeal ovarian tissue aspiration with subsequent oocyte cryopreservation of M2 oocytes and in vitro maturation of immature oocytes. This strategy has been reported by several authors and 2 live births through this strategy have been reported; a 21-year-old with Stage IIIC papillary serous ovarian cancer and a 23-year-old with a recurrent borderline mucinous cystadenoma. The latter patient underwent right salpingo-oophorectomy at the time of her initial diagnosis and then a left salpingo-oophorectomy when she had a complex mass. Ten prophase oocytes were retrieved from normal-appearing ovarian tissue and the oocytes underwent in vitro maturation. Four M2 oocytes were fertilized using intracytoplasmic sperm injection (ICSI) and 3 zygotes were cryopreserved. The patient returned 5 years later, 3 zygotes were thawed and 2 cleavage-stage embryos were transferred resulting in a term, live birth of a healthy child.

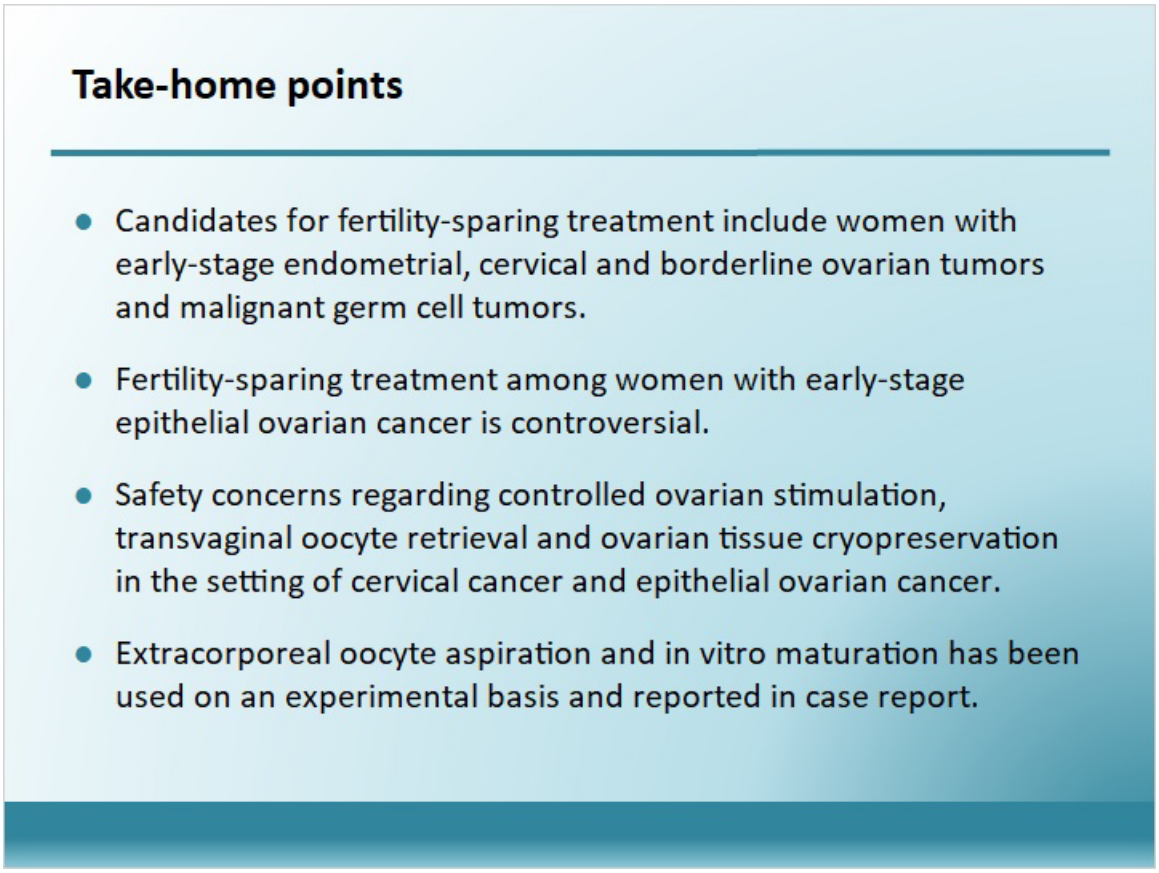
1.20 Alternatives to fertility preservation



Notes:

Women with gynecologic malignancies who desire future fertility should also be counseled regarding alternative options such as use of donor eggs, gestational carrier, and adoption where appropriate.

1.21 Take-home points



Notes:

In summary, candidate for fertility-sparing treatments include women with early-stage endometrial, cervical and borderline ovarian and malignant germ cell tumors. Fertility-sparing treatment among women with early-stage epithelial ovarian cancer is controversial. There are safety concerns regarding controlled ovarian stimulation, transvaginal oocyte retrieval and ovarian tissue cryopreservation in the setting of cervical cancer and epithelial ovarian cancer. Extracorporeal oocyte aspiration and in vitro maturation of prophase oocytes has been used in an experimental basis and reported in case reports.

1.22 Thank you!

Notes:

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