HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Ann Surg Oncol. 2019 May ; 26(5): 1214–1224. doi:10.1245/s10434-019-07156-7.

Young Women with Breast Cancer: Fertility Preservation Options and Management of Pregnancy-Associated Breast Cancer

Nikita M. Shah, MD[1,*], **Dana M. Scott, MD**[2,*], **Pridvi Kandagatla, MD**[1,3], **Molly B. Moravek, MD**[4], **Erin F. Cobain, MD**[5], **Monika L. Burness, MD**[5], and **Jacqueline S. Jeruss, MD, PhD**[1,6,7]

[1]Department of Surgery, University of Michigan, Ann Arbor, Michigan

[2]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan

[3]Department of Surgery, Henry Ford Health System/Wayne State University, Detroit, Michigan

[4]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI

[5]Division of Medical Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

[6]Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

[7]Department of Pathology, University of Michigan, Ann Arbor, Michigan

Abstract

Breast cancer is the most common malignancy in women of childbearing age, with approximately 11,160 cases diagnosed annually in patients under the age of 40. A breast cancer diagnosis in this young patient population can be uniquely complex to navigate in light of the potential morbidity of fertility loss associated with specific gonadotoxic therapies. A multidisciplinary approach to patient care, including oncologists and reproductive specialists, can provide young breast cancer patients with options for fertility preservation. There are well-established options for fertility preservation, and several experimental techniques show promise for clinical translation. Another unique challenge for young breast cancer patients is pregnancy-associated breast cancer (PABC), which occurs in approximately one out of every 3,000 pregnancies. With the appropriate multidisciplinary management, PABC can be diagnosed and treated with minimal morbidity to the mother and the developing fetus. Suggested clinical practice guidelines are presented, which delineate breast cancer treatment recommendations based on pregnancy trimester.

Introduction

Annually, 11,160 young women (< 40 years) are diagnosed with invasive breast cancer in the United States, making it the most common malignancy among women of childbearing

Corresponding Author: Jacqueline S. Jeruss, MD, PhD, Associate Professor of Surgery, Division of Surgical Oncology, Department of Surgery, 1500 East Medical Center Drive, SPC 5916, Ann Arbor, MI 48109, jjeruss@med.umich.edu, Telephone: 951-764-2531, Fax: 734-647-9647.

*Both authors contributed equally to this manuscript.

Disclosures: None

age.[1] The management of breast cancer in young patients is associated with unique challenges.[2] As younger women are not typically undergoing breast cancer screening, this patient population often presents with later stage disease.[3] In addition, younger patients may have distinct survivorship goals, including fertility preservation and pregnancy. Standard therapies used to treat breast cancer can negatively affect reproductive health resulting in ovarian insufficiency, treatment-associated time delay for childbearing, and the inability to breastfeed.[4–6] Also, concerns associated with maintaining future fertility can impact a young patient's willingness to undergo recommended cancer treatments.[2,7] Therefore, at the earliest possible time point, providers should prioritize a discussion about fertility preservation options prior to initiation of cancer treatment.[7–10]

Another challenge associated with the management of young breast cancer patients is pregnancy-associated breast cancer (PABC). PABC (breast cancer diagnosed during pregnancy or within 1 year post-partum) occurs in nearly 1 in 3,000–10,000 pregnancies, with the majority diagnosed during the post-partum period.[11,12] As women are now more frequently delaying childbearing, the incidence of PABC may increase. Though PABC tends to be more advanced at diagnosis, recent studies have shown that outcomes for patients with PABC can be similar to nonpregnant patients when matched for tumor characteristics and stage.[3,13,14] While data about the optimal management of PABC continues to evolve, some guidelines have been established.[10,15,16]

As more is learned about breast cancer in the context of fertility and pregnancy, treatment algorithms are being updated that facilitate increased therapeutic options for providers and patients. Here, we discuss options for fertility preservation, both established and in development, and also detail the current management of PABC, a challenging diagnosis that should be approached by a multidisciplinary clinical team.

IMPLICATIONS FOR BREAST CANCER THERAPY ON FERTILITY

Radiation

The amount of radiation that reaches the ovaries and uterus via scatter during breast/axillary radiation is relatively low; thus, the gonadotoxic effects of radiation during treatment for breast cancer should be minimal.[17] However, due to the potential risk of radiation scatter effects, shielding of the pelvic area should be considered to minimize radiation to reproductive organs, and pregnancy should be delayed until after completion of radiation therapy.18–20

Systemic Therapy

Many chemotherapeutic agents used for breast cancer treatment have a direct impact on fertility as these treatments can lead to temporary or permanent chemotherapy related amenorrhea.[21] Alkylating agents (e.g. cyclophosphamide) have the highest risk of gonadotoxicity with amenorrhea occurring in 40–60% of women <40 years old, and in >80% of women >40 years old when used at higher doses.[6] Anthracyclines are less gonadotoxic than alkylating agents, but are still associated with a high rate of amenorrhea.[22]

Taxanes have been reported to result in amenorrhea when used in conjunction with anthracyclines and cyclophosphamide.[23,24]

The effect of anti-HER2 targeted therapy (e.g. trastuzumab and pertuzumab) has been challenging to assess as these medications are often administered concurrently with chemotherapy. However, recent studies have shown that treatment with trastuzumab may not contribute to amenorrhea.[21,24,25] Currently, it is recommended to delay any attempts for pregnancy for at least seven months after completion of anti-HER2 directed therapy due to risks of teratogenicity.[26]

Endocrine Therapy

There is abundant evidence showing the benefit of adjuvant antihormonal therapy for young premenopausal patients with hormone receptor positive breast cancer using tamoxifen (with or without ovarian suppression) or aromatase inhibitors (with ovarian suppression).[27] Additionally, recent data demonstrating the long-term persistent risk of recurrence for patients with hormone receptor positive breast cancer further supports the recommendation for a 10-year tamoxifen treatment duration for many patients.[28] While tamoxifen treatment has several benefits, this drug is also a known teratogen. Consequently, concerns about fertility and pregnancy have been significantly associated with the lack of tamoxifen initiation and continuation.[29]

Importantly, data regarding the safety of pregnancy after breast cancer has been largely reassuring, though generated from retrospective studies.[14] A recent multicenter case-control study by Lambertini et al., found that pregnancy after treatment for breast cancer, regardless of hormone receptor status, did not impact disease-free survival when compared to the outcomes for nonpregnant patients.[30] At the same time, a prospective study was needed to help providers counsel young hormone receptor positive breast cancer survivors about the safety and timing for an interruption in endocrine therapy to allow for potential pregnancy. Accordingly, the Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) (NCT 02308085) is an ongoing clinical study to establish long-term outcomes regarding the impact of pregnancy for this patient population.[31] This study includes endocrine therapy usage for 18–30 months, followed by a 3-month “wash out” period prior to conception. Patients on the study then have a 2-year window to allow for pregnancy and breastfeeding prior to restarting antihormonal therapy to complete a duration of treatment spanning 5 to 10 years.[32]

FERTILITY PRESERVATION FOR YOUNG BREAST CANCER PATIENTS

Baseline fertility can be evaluated by measuring serum anti-Müllerian hormone (AMH), serum follicle stimulating hormone (FSH) with estradiol in the early follicular phase, and/or antral follicle count by transvaginal ultrasound.[33–36] For women with diminished ovarian reserve or advanced reproductive age, a realistic discussion about the likelihood of successful oocyte retrieval and/or pregnancy should be undertaken prior to pursuing invasive fertility preservation options, including oocyte retrieval and oocyte/embryo cryopreservation. Patients desiring future fertility should also be counseled about options for *in vitro*

fertilization (IVF) with donor oocytes, gestational carrier with native or donor oocytes, and adoption.[17] Table 1 provides an overview of available options for fertility preservation.

Oocyte and/or Embryo Cryopreservation

Oocyte/embryo cryopreservation is the most well-established and successful option for fertility preservation; it is, therefore, the recommended option for women with sufficient ovarian reserve who are medically stable to undergo controlled ovarian stimulation (COS).[37] Recent data show that ovarian stimulation may be implemented at any point in the menstrual cycle, known as a "random start" protocol, which has minimized the time needed for fertility preservation prior to initiation of cancer treatment.[38–42] For patients with a low number of oocytes retrieved in one COS cycle, additional cycles may be performed before and after breast cancer surgery. Multiple small studies show that consecutive COS cycles can be performed successfully within a two-week time frame.[38–42] To minimize potential treatment delays, breast cancer patients interested in fertility preservation should be urgently referred to a reproductive endocrinologist. In a recent retrospective review of 262 breast cancer patients who underwent fertility preservation counseling, there was no difference in time to next cancer treatment between those patients that underwent COS for fertility preservation, and those patients that elected not to proceed with fertility preservation procedures.[43] Additionally, there were no differences found in the incidence of cancer recurrence or survival between the two patient groups.[43]

Ovarian stimulation causes an increase in the level of circulating estrogen, and accordingly, many fertility preservation programs administer an aromatase inhibitor concurrently with treatment to minimize elevations in estrogen levels without compromising cycle outcomes.[44,45] Peak estrogen levels in patients undergoing COS with concurrent letrozole range from 58.4 to 1,166 pg/mL (mean, 406.94 ± 256.64 pg/mL or 1,486.76 ± 942.13 pmol/L).[44] Currently, there is no evidence that the increased circulating estrogen levels associated with COS, with or without letrozole treatment, negatively affects the risk of breast cancer recurrence or overall survival.[43–46] Despite these encouraging results, more recent studies have shown that ovarian stimulation has yielded inferior results among patients with BRCA mutations.[47,48]

Patients have the option for cryopreservation of mature oocytes alone or embryo cryopreservation after oocyte fertilization. Due to improvements in cryopreservation techniques, a frozen oocyte is now considered equivalent to a fresh oocyte,[49] thereby increasing preservation options for patients who are not prepared to preserve embryos. Live birth rates and perinatal outcomes are similar with frozen embryo transfers and frozen oocyte-derived embryo transfers (25% and 25.1%, respectively).[50]

Experimental Approaches

GnRH Agonist Administration—The concurrent administration of GnRH agonists (e.g. goserelin, leuprolide, triptorelin) during treatment with chemotherapy has been considered an experimental approach for fertility preservation in the past, and there has been significant controversy regarding the efficacy of this treatment strategy.[41,51–55] Recently, a meta-analysis of the five major trials assessing the impact of GnRH agonists demonstrated a

significantly lower rate of premature ovarian insufficiency (POI) for patients that received GnRH agonist therapy when compared to patients that received chemotherapy alone (14.1% versus 30.9%, respectively; P=0.001).[56] Additionally, there was a significantly higher pregnancy rate following treatment for the GnRH agonist therapy group, when compared to patients treated with chemotherapy alone (10.3% versus 5.5%, respectively; P=0.03).[56] Cancer outcomes, including disease-free and overall survival, did not differ between the treatment groups.[56] The recent randomized controlled trials studying the effectiveness of GnRH agonist for fertility preservation are summarized in Table 2. Recent guidelines recommend consideration of GnRH agonist administration for preservation of ovarian function, especially when other fertility preservation methods are not suitable options for the patient.[8,9,57]

Ovarian Tissue Cryopreservation—Ovarian tissue cryopreservation (OTC) involves surgical excision of ovarian tissue (typically via laparoscopic unilateral oophorectomy), followed by cryopreservation of carefully prepared strips of ovarian tissue.[17,41] OTC potentially offers a mechanism to preserve thousands of follicles with a single procedure. When childbearing is desired, autologous transplantation of the cryopreserved ovarian tissue can be performed. A recently published meta-analysis looking at studies of ovarian tissue transplantation found a cumulative clinical birth rate of 57.5%.[58] Currently, there is concern for potential reseeding of malignant cells with autologous ovarian tissue transplantation, particularly in the setting of hematologic malignancies and BRCA mutation carriers.[59] Alternatively, *in vitro* follicle maturation, discussed below, offers another utilization for OTC.[17]

In vitro follicle maturation—In vitro follicle maturation (IVM) is a mechanism to foster the nascent development of immature oocytes obtained from either OTC or transvaginal retrieval of immature oocytes (a potential option for women unable or unwilling to undergo COS) to then facilitate IVF.[60] There are live births attributed to each retrieval method, and data regarding the safety and success of these methods continues to evolve in both the laboratory and clinical settings.[61]

Use of Retrievable Hydrogels—Concerns regarding follicular atresia after ovarian transplantation and re-seeding malignant cells have limited the widespread use of OTC. Biomaterial hydrogels are currently under investigation as an alternate method to facilitate fertility preservation and restoration of endocrine function.[61,62] Using these techniques, nascent ovarian follicles are encapsulated in hydrogels. They are subsequently transplanted in a heterotopic site in the patient, allowing for *in vivo* maturation. An early study in a murine model demonstrated survival of multiple follicle populations with minimal evidence of tumor re-seeding.[63] This technique continues to evolve and shows promise for premenarchal patients and patients unable to undergo COS.

Preimplantation Genetic Diagnosis

Reproductive-aged women diagnosed with breast cancer should be offered a genetic evaluation to screen for hereditary breast and ovarian cancer (HBOC) gene mutations.[64,65] In addition to affecting a woman's treatment planning and future screening, the

identification of an HBOC mutation can have implications on fertility. If desired by the patient, propagation of the HBOC gene mutation may be prevented by performing preimplantation genetic diagnosis (PGD) for monogenic diseases on biopsies from cryopreserved embryos or cryopreserved oocyte-derived embryos.[41] Embryos that do not harbor the HBOC gene mutation can then potentially be selected for implantation. While personal opinions about PGD may vary, it is important that the availability of the technology be discussed and offered to allow informed patient decision-making.

PREGNANCY-ASSOCIATED BREAST CANCER

Diagnosis and Workup

Workup of a suspicious breast mass should proceed similarly for pregnant, post-partum, and non-pregnant patients. Mammogram and ultrasound both are sensitive and specific during pregnancy.[66,67] With appropriate abdominal shielding, mammography is associated with minimal risk to the developing fetus.[68] Breast ultrasound is particularly useful as it can distinguish between cystic and solid lesions, and is safe during pregnancy.[69] Though gadolinium contrast is considered teratogenic,[67] magnetic resonance imaging (MRI) without gadolinium contrast can help evaluate the breast during pregnancy.[68] While there are no published reports of harmful effects of MRI on the fetus and without long-term prospective safety data, MRI should be used with appropriate caution, particularly during the first trimester when fetal organogenesis occurs.[70] In the post-partum setting, contrast-enhanced MRI may be performed, with the understanding that it can be difficult to distinguish lactational changes from a disease process.[71]

Staging scans should be performed when suspicion of metastatic disease is high and will change clinical management. Metastatic workup during pregnancy should include a chest x-ray, liver ultrasound, and non-contrast skeletal MRI.[72] A recent study has shown that whole body MRI may be a promising option for the staging of pregnant women diagnosed with breast cancer.[73] There is some limited data to suggest that the fetal radiation dose is low with (18)F-FDG PET-only and (18)F-FDG PET/MR, particularly during the later stages of pregnancy, though there is insufficient data to establish recommendations regarding the use of PET scanning for cancer staging during pregnancy.[74,75] Radiologists should be involved early on in the formulation of the diagnostic strategy to help minimize the cumulative fetal toxicity, reduce radiation exposure, and optimize diagnostic accuracy.

General Management Principles

Once a PABC diagnosis is made, the patient should be managed by a multidisciplinary clinical team, including oncologists, high-risk obstetric specialists and neonatologists.[10,16] The treatment goals for pregnant patients should not differ from that of non-pregnant patients, in that when possible, breast cancers should be treated with curative intent. However, the treatment team and the patient must understand the potential impact of the available therapies on the developing fetus/infant. For patients with PABC, in addition to standard oncologic factors including disease stage and tumor receptor status, the trimester of pregnancy impacts treatment options and sequencing of therapies (Table 3).

Treatment Options and Pregnancy

Surgery—Surgery can be performed during any trimester of pregnancy, though risk of pregnancy loss may be higher during the first trimester.[76] Exposure to modern anesthetic agents has not been associated with teratogenic effects at any gestational time-point, including the first trimester, when organogenesis occurs.[77] At pre-viable gestational ages (prior to 23–24 weeks), fetal heart tones should be documented before and after breast cancer surgery. Once the fetus is considered viable, fetal monitoring should include electronic fetal heart rate and uterine contraction monitoring before and after surgery. Intraoperative fetal monitoring should be used only in cases in which the patient and providers are prepared for emergency cesarean delivery if fetal distress is detected.[76]

According to the National Comprehensive Cancer Network (NCCN) Guidelines, breast conservation is feasible during pregnancy, but radiation therapy, an adjunct to breast conservation, is contraindicated throughout pregnancy.[15] This contraindication limits the feasibility of a lumpectomy during the first trimester, a time when chemotherapy is also contraindicated. Additionally, the lactation changes that occur during pregnancy can add to the complexity of breast cancer diagnostics, making the estimation of tumor size more difficult to determine.[67,71] Together, the increased complexity of establishing an accurate preoperative tumor size, and the contraindication of radiation therapy, make successful lumpectomy more challenging to achieve during pregnancy, thus supporting surgical treatment with mastectomy. However, a lumpectomy can be offered to appropriately selected patients for whom the initiation of radiation would not be significantly delayed, including patients undergoing neoadjuvant/adjuvant therapy in the later second or third trimesters, or patients diagnosed in the third trimester for whom radiation therapy can be safely initiated after delivery.[15]

Although there are no established guidelines regarding reconstructive surgery during pregnancy, reconstruction is generally delayed until the patient is post-partum, to minimize operative time and potential surgical complications during pregnancy.[78] However, there are small studies demonstrating the safety of immediate reconstruction among these patients.[79,80] Issues with breast symmetry may also be best addressed after post-lactational involution.

NCCN Guidelines state that axillary staging may be accomplished safely during pregnancy with a sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND), but decisions should be made on a patient-to-patient basis.[15] Han et al. showed the safety of SLNB in pregnant patients, with a comparable axillary recurrence rate to non-pregnant patients.[81] Lymphoscintigraphy with Technetium-99 is relatively safe and accurate for the identification of the axillary sentinel nodes.[82] Measurements of radiation exposure to the fetus indicate doses well below the safety threshold.[83–85] Conversely, sentinel lymph node identification with blue dye injection has limited safety data in pregnancy, and given the risk of anaphylaxis (isosulfan blue) and unknown teratogenicity associated with blue dyes (both isosulfan and methylene blue), blue dyes are contraindicated in pregnancy.[86,87]

Radiation—Radiation therapy is linked to adverse fetal outcomes, including intrauterine growth restriction, cognitive impairment, and childhood malignancies.[88] Radiation exposure

in the first trimester is also associated with pregnancy loss and congenital malformations.[88] Current recommendations are to delay radiation therapy until the postpartum period.

Lactation is possible after breast radiation therapy. In a literature review, approximately 50% of patients that received breast radiation therapy were subsequently able to breastfeed, however these patients were found to have a decrease in milk production from the treated breast.[89] The non-radiated breast should be unaffected in terms of milk production. To date, a small number of case reports have shown evidence of changes in the biochemical properties of the milk produced from the treated breast following breast radiation therapy.[90]

Systemic Therapy—Chemotherapy recommendations should reflect standard guidelines based on tumor subtype, size, and nodal status. Chemotherapy is avoided in the first trimester, due to the risk of miscarriage and fetal congenital malformations.[91] Consequently, patients with first-trimester PABC, for whom treatment with chemotherapy is indicated, can be offered termination. Chemotherapy administration in the second and third trimester increases risk of preterm delivery and small-for-gestational-age-development, yet studies dating back to the 1980s have shown favorable long-term outcomes for exposed fetuses.[92,93] In addition, studies have shown no neurodevelopmental or cardiac toxicities in offspring exposed to chemotherapy in utero after the first trimester.[94–96] Chemotherapy should be discontinued by 35 to 37 weeks of pregnancy to minimize hematologic toxicity prior to delivery.

Most chemotherapy safety data is derived from anthracycline-based regimens (Adriamycin, Cyclophosphamide [AC]; Epirubicin, Cyclophosphamide [EC]; Fluorouracil, Adriamycin, Cyclophosphamide [FAC]; or Fluorouracil, Epirubicin, Cyclophosphamide [FEC]). As a result, these are the mainstays of chemotherapy treatment options during pregnancy.[97–100] There are some data from case reports suggesting taxanes may be safe for use during pregnancy.[98,101,102] However, NCCN guidelines recommend avoiding the general use of taxane-based regimens during pregnancy due to the limited safety data.[15] Use of weekly paclitaxel may be acceptable in certain clinical situations after the first trimester, such as when anthracyclines are contraindicated.[10] Many of the anti-emetics frequently used to treat chemotherapy-induced nausea and vomiting are generally considered safe for use during pregnancy, including promethazine, selective serotonin (5-HT) antagonists, and neurokinin 1 (NK1) antagonists. Safe use of granulocyte colony stimulating factor (G-CSF) during pregnancy has also been reported,[103] although can be avoided by sequential administration of single-agent chemotherapies.

Administration of anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab) during pregnancy is contraindicated during all trimesters. Both agents have been associated with fetal teratogenicity.[10] Trastuzumab has been linked to oligohydramnios and pulmonary hypoplasia.[26,104] The toxicity of pertuzumab during human pregnancy is unknown, but administration to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and fetal death at higher levels of exposure.[105] Endocrine therapy is also contraindicated for use during pregnancy due to associated teratogenicity.[106] Regarding lactation, the majority of systemic therapies used to treat breast cancer can be excreted in breast milk. Although the excreted drug levels found in breast milk are at approximately 2%

of the maternal dose, as many systemic agents are cytotoxic, breastfeeding during treatment with systemic therapy is not recommended.[91]

SUMMARY

The management of breast cancer in reproductive-aged women is associated with a unique complexity when compared to the management of postmenopausal patients. In conjunction with the standard issues surrounding treatment planning, providers must be equipped to address a young patient's reproductive goals. Young patients who are interested in fertility preservation require time-sensitive counseling and access to fertility preservation options. Women with PABC should have treatment plans tailored appropriately to the trimester at diagnosis and the disease subtype. Treatment decisions are best made collaboratively in a multidisciplinary setting, including the patient and her oncologic and obstetric team. While these clinical situations can be challenging, the translation of medical science continues to facilitate the expansion of treatment options to help improve the outcomes for both fertility preservation and PABC.

Acknowledgements

The authors thank Zachary Pascoe for helpful discussions regarding manuscript preparation.

Grant Support: The authors acknowledge financial support from the NIH R01CA214384 (to J.S. Jeruss), A Sister's Hope Foundation, (J.S.Jeruss), and NIH T32CA009672 (J.S.Jeruss and P. Kandagatla).

References

1. Society AC. Breast Cancer Facts & Figures. In: Society AC, ed. Atlanta2017.
2. Rosenberg SM, Newman LA, Partridge AH. Breast Cancer in Young Women: Rare Disease or Public Health Problem? JAMA Oncol. 10 2015;1(7):877–878. [PubMed: 26204453]
3. Pavlidis N, Pentheroudakis G. The pregnant mother with breast cancer: diagnostic and therapeutic management. Cancer Treat Rev. 10 2005;31(6):439–447. [PubMed: 15946802]
4. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 3 5 2015;372(10):923–932. [PubMed: 25738668]
5. Christinat A, Pagani O. Fertility after breast cancer. Maturitas. 11 2012;73(3):191–196. [PubMed: 23020991]
6. Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 7 2017;29(4):243–252. [PubMed: 28463857]
7. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 4 10 2014;32(11):1151–1156. [PubMed: 24567428]
8. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 7 1 2018;36(19):1994–2001. [PubMed: 29620997]
9. Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast. 10 2017;35:203–217. [PubMed: 28822332]
10. Peccatori FA, Azim HA Jr., Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 10 2013;24 Suppl 6:vi160–170. [PubMed: 23813932]
11. Pavlidis NA. Coexistence of pregnancy and malignancy. Oncologist. 2002;7(4):279–287. [PubMed: 12185292]

12. Stensheim H, Moller B, van Dijk T, Fossa SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol. 1 1 2009;27(1): 45–51. [PubMed: 19029418]
13. Johansson ALV, Andersson TM, Hsieh CC, et al. Tumor characteristics and prognosis in women with pregnancy-associated breast cancer. Int J Cancer. 4 1 2018;142(7):1343–1354. [PubMed: 29168177]
14. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 11 2016;160(2):347–360. [PubMed: 27683280]
15. Network NCC. Breast Cancer Version (1.2018). 2018; https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 2018.
16. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 11 2015;1(8):1145–1153. [PubMed: 26247818]
17. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2 26 2009;360(9):902–911. [PubMed: 19246362]
18. Antypas C, Sandilos P, Kouvaris J, et al. Fetal dose evaluation during breast cancer radiotherapy. Int J Radiat Oncol Biol Phys. 3 1 1998;40(4):995–999. [PubMed: 9531386]
19. Mazonakis M, Varveris H, Damilakis J, Theoharopoulos N, Gourtsoyiannis N. Radiation dose to conceptus resulting from tangential breast irradiation. Int J Radiat Oncol Biol Phys. 2 1 2003;55(2):386–391. [PubMed: 12527052]
20. Rodriguez-Wallberg KA, Oktay K. Fertility preservation during cancer treatment: clinical guidelines. Cancer Manag Res. 2014;6:105–117. [PubMed: 24623991]
21. Ruddy KJ, Guo H, Barry W, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). Breast Cancer Res Treat. 6 2015;151(3):589–596. [PubMed: 25981899]
22. Ganz PA, Land SR, Geyer CE Jr., et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol. 3 20 2011;29(9):1110–1116. [PubMed: 21300930]
23. Zhao J, Liu J, Chen K, et al. What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. Breast Cancer Res Treat. 5 2014;145(1):113–128. [PubMed: 24671358]
24. Lambertini M, Campbell C, Bines J, et al. Adjuvant Anti-HER2 Therapy, Treatment-Related Amenorrhea, and Survival in Premenopausal HER2-Positive Early Breast Cancer Patients. J Natl Cancer Inst. 6 5 2018.
25. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. Cancer. 2 15 2010;116(4):791–798. [PubMed: 20052714]
26. Zagouri F, Sergentanis TN, Chrysikos D, Papadimitriou CA, Dimopoulos MA, Bartsch R. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res Treat. 1 2013;137(2):349–357. [PubMed: 23242615]
27. Francis PA, Pagani O, Fleming GF, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med. 7 12 2018;379(2):122–137. [PubMed: 29863451]
28. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 11 9 2017;377(19):1836–1846. [PubMed: 29117498]
29. Llarena NC, Estevez SL, Tucker SL, Jeruss JS. Impact of Fertility Concerns on Tamoxifen Initiation and Persistence. J Natl Cancer Inst. 10 2015;107(10).
30. Lambertini M, Kroman N, Ameye L, et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. J Natl Cancer Inst. 4 1 2018;110(4):426–429. [PubMed: 29087485]
31. IBCSG 48–14 POSITIVE Trial. http://www.ibcsg.org/Public/Health_Professionals/Open_Trials/ibcsg_48-14_positive/Pages/IBCSG48-14POSITIVE.aspx. Accessed May 15, 2018.
32. Pagani O, Ruggeri M, Manunta S, et al. Pregnancy after breast cancer: Are young patients willing to participate in clinical studies? Breast. 6 2015;24(3):201–207. [PubMed: 25662412]

33. van Rooij IA, Broekmans FJ, te Velde ER, et al. Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve. Hum Reprod. 12 2002;17(12):3065–3071. [PubMed: 12456604]
34. Freour T, Barriere P, Masson D. Anti-mullerian hormone levels and evolution in women of reproductive age with breast cancer treated with chemotherapy. Eur J Cancer. 3 2017;74:1–8. [PubMed: 28135602]
35. Dezellus A, Barriere P, Campone M, et al. Prospective evaluation of serum anti-Mullerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer. Eur J Cancer. 7 2017;79:72–80. [PubMed: 28463758]
36. Anderson RA, Mansi J, Coleman RE, Adamson DJA, Leonard RCF. The utility of anti-Mullerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer. Eur J Cancer. 12 2017;87:58–64. [PubMed: 29117576]
37. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 7 1 2013;31(19): 2500–2510. [PubMed: 23715580]
38. von Wolff M, Thaler CJ, Frambach T, et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril. 10 2009;92(4):1360–1365. [PubMed: 18930226]
39. Ozkaya E, San Roman G, Oktay K. Luteal phase GnRHa trigger in random start fertility preservation cycles. J Assist Reprod Genet. 6 2012;29(6):503–505. [PubMed: 22492220]
40. Sonmezer M, Turkcuoglu I, Coskun U, Oktay K. Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles. Fertil Steril. 5 2011;95(6):2125 e2129–2111.
41. Practice Committee of American Society for Reproductive M. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 11 2013;100(5):1214–1223. [PubMed: 24011612]
42. Bedoschi GM, de Albuquerque FO, Ferriani RA, Navarro PA. Ovarian stimulation during the luteal phase for fertility preservation of cancer patients: case reports and review of the literature. J Assist Reprod Genet. 8 2010;27(8):491–494. [PubMed: 20455017]
43. Moravek MB, Confino R, Smith KN, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril. 2 2018;109(2):349–355. [PubMed: 29338854]
44. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 6 1 2008;26(16):2630–2635. [PubMed: 18509175]
45. Kim J, Turan V, Oktay K. Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer. J Clin Endocrinol Metab. 4 2016;101(4): 1364–1371. [PubMed: 26751194]
46. Ayhan A, Salman MC, Celik H, Dursun P, Ozyuncu O, Gultekin M. Association between fertility drugs and gynecologic cancers, breast cancer, and childhood cancers. Acta Obstet Gynecol Scand. 12 2004;83(12):1104–1111. [PubMed: 15548140]
47. Lambertini M, Goldrat O, Ferreira AR, et al. Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. Ann Oncol. 1 1 2018;29(1):237–243. [PubMed: 29045555]
48. Turan V, Bedoschi G, Emirdar V, Moy F, Oktay K. Ovarian Stimulation in Patients With Cancer: Impact of Letrozole and BRCA Mutations on Fertility Preservation Cycle Outcomes. Reprod Sci. 1 2018;25(1):26–32. [PubMed: 28874104]
49. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 9 2010;25(9):2239–2246. [PubMed: 20591872]
50. Ho JR, Woo I, Louie K, et al. A comparison of live birth rates and perinatal outcomes between cryopreserved oocytes and cryopreserved embryos. J Assist Reprod Genet. 10 2017;34(10):1359–1366. [PubMed: 28718080]
51. Chen H, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev. 11 9 2011(11):CD008018. [PubMed: 22071842]

52. Bedaiwy MA, Abou-Setta AM, Desai N, et al. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. Fertil Steril. 3 1 2011;95(3):906–914 e901–904. [PubMed: 21145541]
53. Yang B, Shi W, Yang J, 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. 4 2013;22(2):150–157. [PubMed: 23298851]
54. Bai F, Lu Y, Wu K, 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 (Basel). 3 2017;12(1):48–52. [PubMed: 28611542]
55. Lambertini M, Ceppi M, Poggio F, 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. 12 2015;26(12):2408–2419. [PubMed: 26347105]
56. Lambertini M, Moore HCF, Leonard RCF, 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. 7 1 2018;36(19):1981–1990. [PubMed: 29718793]
57. Lambertini M, Cinquini M, Moschetti I, 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. 1 2017;71:25–33. [PubMed: 27940355]
58. Pacheco F, Oktay K. Current Success and Efficiency of Autologous Ovarian Transplantation: A Meta-Analysis. Reprod Sci. 8 2017;24(8):1111–1120. [PubMed: 28701069]
59. Meirow D, Hardan I, Dor J, et al. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. Hum Reprod. 5 2008;23(5):1007–1013. [PubMed: 18344563]
60. Telfer EE, McLaughlin M, Ding C, Thong KJ. A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin. Hum Reprod. 5 2008;23(5):1151–1158. [PubMed: 18326514]
61. Xu M, Kreeger PK, Shea LD, Woodruff TK. Tissue-engineered follicles produce live, fertile offspring. Tissue Eng. 10 2006;12(10):2739–2746. [PubMed: 17518643]
62. Laronda MM, Duncan FE, Hornick JE, et al. Alginate encapsulation supports the growth and differentiation of human primordial follicles within ovarian cortical tissue. J Assist Reprod Genet. 8 2014;31(8):1013–1028. [PubMed: 24845158]
63. Rios PD, Kniazeva E, Lee HC, et al. Retrievable hydrogels for ovarian follicle transplantation and oocyte collection. Biotechnol Bioeng. 8 2018;115(8):2075–2086. [PubMed: 29704433]
64. Daly Mary B., RP, Berry Michael P., Buys Saundra S., Friedman Susan, Garber Judy E., Hutton Mollie L., Kauff Noah D., Khan Seema, Klein Catherine, Kohlmann Wendy, Kurian Allison W., Laronga Christine, Litton Jennifer K., Madlensky Lisa, Mak Julie S., Merajver Sofia D., Offit Kenneth, Pal Tuya, Pederson Holly J., Reiser Gwen, Kristen Mahoney Shannon, Thaker Premal, Visvanathan Kala, Weitzel Jeffrey N., Wick Myra J., Wisiniski Kari B.. Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018. 2017; https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed May 14, 2018.
65. Committee on Practice Bulletins-Gynecology CoGSoGO. Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome. Obstet Gynecol. 9 2017;130(3):e110–e126. [PubMed: 28832484]
66. Robbins J, Jeffries D, Roubidoux M, Helvie M. Accuracy of diagnostic mammography and breast ultrasound during pregnancy and lactation. AJR Am J Roentgenol. 3 2011;196(3):716–722. [PubMed: 21343518]
67. Carmichael H, Matsen C, Freer P, et al. Breast cancer screening of pregnant and breastfeeding women with BRCA mutations. Breast Cancer Res Treat. 4 2017;162(2):225–230. [PubMed: 28138892]

68. Wang PI, Chong ST, Kielar AZ, et al. Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations. AJR Am J Roentgenol. 4 2012;198(4):778–784. [PubMed: 22451541]
69. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer. 12 2010;46(18):3158–3168. [PubMed: 20932740]
70. Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. Semin Perinatol. 10 2013;37(5):301–304. [PubMed: 24176150]
71. Vashi R, Hooley R, Butler R, Geisel J, Philpotts L. Breast imaging of the pregnant and lactating patient: imaging modalities and pregnancy-associated breast cancer. AJR Am J Roentgenol. 2 2013;200(2):321–328. [PubMed: 23345353]
72. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2 11 2012;379(9815):570–579. [PubMed: 22325662]
73. Peccatori FA, Codacci-Pisanelli G, Del Grande M, Scarfone G, Zugni F, Petralia G. Whole body MRI for systemic staging of breast cancer in pregnant women. Breast. 10 2017;35:177–181. [PubMed: 28756339]
74. Takalkar AM, Khandelwal A, Lokitz S, Lilien DL, Stabin MG. 18F-FDG PET in pregnancy and fetal radiation dose estimates. J Nucl Med. 7 2011;52(7):1035–1040. [PubMed: 21680687]
75. Zanotti-Fregonara P, Laforest R, Wallis JW. Fetal Radiation Dose from 18F-FDG in Pregnant Patients Imaged with PET, PET/CT, and PET/MR. J Nucl Med. 8 2015;56(8):1218–1222. [PubMed: 26089550]
76. Gynecologists ACoOa. Nonobstetric Surgery During Pregnancy. 2017;129:777–778.
77. Cheek TG, Baird E. Anesthesia for nonobstetric surgery: maternal and fetal considerations. Clin Obstet Gynecol. 12 2009;52(4):535–545. [PubMed: 20393407]
78. Keleher AJ, Theriault RL, Gwyn KM, et al. Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg. 1 2002;194(1):54–64. [PubMed: 11800340]
79. Caragacianu DL, Mayer EL, Chun YS, et al. Immediate breast reconstruction following mastectomy in pregnant women with breast cancer. J Surg Oncol. 8 2016;114(2):140–143. [PubMed: 27392534]
80. Lohsiriwat V, Peccatori FA, Martella S, et al. Immediate breast reconstruction with expander in pregnant breast cancer patients. Breast. 10 2013;22(5):657–660. [PubMed: 23871328]
81. Han SN, Amant F, Cardonick EH, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Res Treat. 4 2018;168(2):551–557. [PubMed: 29235045]
82. Shlensky V, Hallmeyer S, Juarez L, Parilla BV. Management of Breast Cancer during Pregnancy: Are We Compliant with Current Guidelines? AJP Rep. 1 2017;7(1):e39–e43. [PubMed: 28255521]
83. Spanheimer PM, Graham MM, Sugg SL, Scott-Conner CE, Weigel RJ. Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. Ann Surg Oncol. 5 2009;16(5):1143–1147. [PubMed: 19267158]
84. Keleher A, Wendt R 3rd, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. Breast J. Nov-Dec 2004;10(6):492–495. [PubMed: 15569204]
85. Pandit-Taskar N, Dauer LT, Montgomery L, St Germain J, Zanzonico PB, Divgi CR. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med. 7 2006;47(7):1202–1208. [PubMed: 16818956]
86. Gentilini O, Cremonesi M, Toesca A, et al. Sentinel lymph node biopsy in pregnant patients with breast cancer. Eur J Nucl Med Mol Imaging. 1 2010;37(1):78–83. [PubMed: 19662412]
87. Gropper AB, Calvillo KZ, Dominici L, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol. 8 2014;21(8):2506–2511. [PubMed: 24756813]
88. Valentin J Biological effects after prenatal irradiation (embryo and fetus): ICRP Publication 90 Approved by the Commission in October 2002. Annals of the ICRP. 2003;33(1–2):1–206.
89. Deckers S, Amant F. Breast cancer in pregnancy: a literature review. Facts Views Vis Obgyn. 2009;1(2):130–141. [PubMed: 25478078]

90. Leal SC, Stuart SR, Carvalho Hde A. Breast irradiation and lactation: a review. Expert Rev Anticancer Ther. 2 2013;13(2):159–164. [PubMed: 23406557]
91. Azim HA Jr., L Del Mastro, Scarfone G, Peccatori FA. Treatment of breast cancer during pregnancy: regimen selection, pregnancy monitoring and more. Breast. 2 2011;20(1):1–6. [PubMed: 21111624]
92. Azim HA Jr., Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. Cancer Treat Rev. 4 2010;36(2):101–109. [PubMed: 20015593]
93. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 3 2018;19(3):337–346. [PubMed: 29395867]
94. Amant F, Van Calsteren K, Halaska MJ, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol. 3 2012;13(3):256–264. [PubMed: 22326925]
95. Cardonick EH, Gringlas MB, Hunter K, Greenspan J. Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy-exposed children with nonexposed controls. Am J Obstet Gynecol. 5 2015;212(5):658 e651–658. [PubMed: 25434835]
96. Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. N Engl J Med. 11 5 2015;373(19):1824–1834. [PubMed: 26415085]
97. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A. Breast cancer during pregnancy: maternal and fetal outcomes. Cancer J. Jan-Feb 2010;16(1):76–82. [PubMed: 20164696]
98. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 9 2012;13(9):887–896. [PubMed: 22902483]
99. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer. 9 15 2006;107(6):1219–1226. [PubMed: 16894524]
100. Peccatori FA, Azim HA Jr., Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat. 6 2009;115(3):591–594. [PubMed: 18712595]
101. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. Clin Breast Cancer. 2 2013;13(1):16–23. [PubMed: 23122538]
102. Cardonick E, Bhat A, Gilmandyar D, Somer R. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. Ann Oncol. 12 2012;23(12):3016–3023. [PubMed: 22875836]
103. Gerald G, Briggs RKF, Towers Craig V., Forinash Alicia B.. Drugs in Pregnancy and Lactation. 11 ed: Wolters Kluwer; 2017.
104. Lambertini M, Peccatori FA, Azim HA Jr. Targeted agents for cancer treatment during pregnancy. Cancer Treat Rev. 4 2015;41(4):301–309. [PubMed: 25795021]
105. Maly JJ, Macrae ER. Pertuzumab in Combination with Trastuzumab and Chemotherapy in the Treatment of HER2-Positive Metastatic Breast Cancer: Safety, Efficacy, and Progression Free Survival. Breast Cancer (Auckl). 2014;8:81–88. [PubMed: 24855372]
106. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R. Use of tamoxifen before and during pregnancy. Oncologist. 2011;16(11):1547–1551. [PubMed: 22020212]
107. Leonard RCF, Adamson DJA, Bertelli G, et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol. 8 1 2017;28(8):1811–1816. [PubMed: 28472240]
108. Gerber B, von Minckwitz G, Stehle H, 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. 6 10 2011;29(17):2334–2341. [PubMed: 21537042]
109. Lambertini M, Boni L, Michelotti A, 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. 12 22–29 2015;314(24):2632–2640. [PubMed: 26720025]

110. Munster PN, Moore AP, Ismail-Khan R, 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. 2 10 2012;30(5):533–538. [PubMed: 22231041]

Synopsis:

Young breast cancer patients face the potential impact of treatment on future fertility. Additionally, a subset of patients will navigate the challenges of breast cancer treatment during pregnancy or during the post-partum period. Suggested guidelines are provided to address reproductive health in conjunction with a breast cancer diagnosis.

Table 1.

Fertility preservation options for the premenopausal breast cancer patient

Fertility Preservation Approach	Status
Oocyte and/or Embryo Cryopreservation	
• "Random start" protocols possible at any point in menstrual cycle causing minimal treatment delays • Concurrent AI therapy can help temper estrogen levels • Equivalent live birth rates with frozen embryos (FET) and frozen oocyte-derived embryos transfers (FOET) • Preimplantation genetic diagnosis available for patients with genetic mutations	Most well-established and successful method of fertility preservation • Live birth rates: o FET: 25% o FOET: 25.1%
GnRH Agonist Administration	
• Concurrent administration with chemotherapy results in lower rate of primary ovarian insufficiency (POI) • Controversy regarding fertility preservation efficacy • Recent meta-analysis showed increased pregnancy rate among women who received a GnRH agonist with chemotherapy when compared to patients who received chemotherapy alone	• Implementation currently considered for ovarian function preservation • Recent data suggests safety and efficacy in preventing POI and increasing pregnancy rates
Ovarian Tissue Cryopreservation (OTC)	
• Experimental technique involving surgical excision of ovarian tissue for cryopreservation • Autologous transplantation of tissue can be performed when childbearing is desired • Potential concern for tumor reseeding with tissue transplantation • Tissue can potentially be used for *in vitro* follicle maturation	• Emerging approach that has resulted in live births
Emerging Technologies for Follicle Maturation	
In Vitro Follicle Maturation	
• Mechanism to mature oocytes retrieved from OTC or transvaginal oocyte retrieval • Avoids reimplantation of ovarian tissue • Has resulted in live births	
Retrievable Hydrogels	
• Nascent ovarian follicles encapsulated in hydrogeHydrogels transplanted in a heterotopic site, allowing *in vivo* maturation • Promising results in murine models	

Table 2.

Major GnRH agonist trials

Trial	GnRH agonist	Outcome (versus controls)
POEMS/SWOG S0230[4]	Goserelin 3.6mg subcutaneous	Premature ovarian insufficiency: 8% versus 22% (P=0.04)
		Rates of pregnancy: 21% versus 11% (P=0.03)
Anglo Celtic Group OPTION	Goserelin 3.6mg subcutaneous	Premature ovarian insufficiency: 18.5% versus 34.8% (P=0.048)
		Rates of pregnancy: not reported
GBG 37 ZORO[108]	Goserelin 3.6mg subcutaneous	Resumption of menstruation: 70.0% versus 56.7% (P=0.284)
PROMISE-GIM6[109]	Triptorelin 3.75mg intramuscular	Premature ovarian insufficiency: 8.9% versus 25.9% (P=0.001)
Munster PN, Moore AP, Ismail-Khan R (2012)[110]	Triptorelin 3.75mg intramuscular	Amenorrhea rates: 88% versus 90% (P=.36)

*Note all GnRH agonists were administered with the same frequency: 1 week prior to chemotherapy and every 4 weeks during chemotherapy

Table 3.

Clinical practice guidelines for treatment of breast cancer during pregnancy

Trimester	Recommendation
	Surgery
First	- **Monitoring:** Fetal heart tones before and after surgery - **Type:** Mastectomy/axillary staging[a] recommended

Second	- Favorable trimester for non-emergent surgery
	- **Monitoring:**
	  - Before viability (23–24 weeks): fetal heart tones before and after surgery
	  - After viability: monitor fetal heart tracing & tocometry before and after surgery
	  - Consider intraoperative fetal monitoring if:
	  - Intraoperative emergent cesarean delivery is feasible as necessary
	  - Patient has been counseled/consented for cesarean delivery
	- **Type:** Mastectomy/axillary staging[a] recommended
	  - For appropriately selected surgical candidates also being treated with neoadjuvant/adjuvant therapy, can consider lumpectomy with completion of radiation postpartum

Third	- **Monitoring:** Monitor fetal heart tracing & tocometry before and after surgery - Consider intraoperative fetal monitoring as noted for second trimester - **Type:** Mastectomy or lumpectomy with completion of radiation postpartum (for appropriate surgical candidates)/axillary staging[a] recommended
Overall	- Recommend delaying reconstruction until postpartum period
Systemic Therapy	
First	- Avoid due to risk of miscarriage and fetal congenital malformations

Second
Third
	- Chemotherapy generally considered safe without long-term complications
	  - Possible increased risk of preterm delivery, small for gestational age infants
	- Anthracycline-based regimens have the most safety data
	- Insufficient safety data for general use of taxanes; weekly administration of paclitaxel is acceptable if clinically indicated
	- Anti-HER2/neu directed therapy (trastuzumab and pertuzumab) not recommended
	  - Risks of oligohydramnios and pulmonary hypoplasia
	- Discontinue chemotherapy by 35–37 weeks to minimize hematologic toxicity

Overall	- Antihormonal therapy contraindicated during all trimesters
Radiation Therapy	

First
Second
Third
	- Absolutely contraindicated in all trimesters due to fetal toxicity:
	  - 1st trimester exposure: Pregnancy loss and congenital malformations
	  - 2nd/3rd trimester exposure: Intrauterine growth restriction, cognitive impairment, fetal death, increased risk of childhood malignancies

[a]NCCN Guidelines state that axillary staging can be performed using ALND or SLNB with technetium 99m sulfur colloid, depending on the individual patient's clinical presentation. However, blue dyes used for SLNB are contraindicated in pregnancy secondary to the risk of anaphylaxis and unknown teratogenicity.[15]