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

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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

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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 $1,486.76 \pm 942.13$ 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 reseedling 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.

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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	
<ul style="list-style-type: none"> • “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 	<p>Most well-established and successful method of fertility preservation</p> <ul style="list-style-type: none"> • Live birth rates: <ul style="list-style-type: none"> o FET: 25% o FOET: 25.1%
GnRH Agonist Administration	
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Implementation currently considered for ovarian function preservation • Recent data suggests safety and efficacy in preventing POI and increasing pregnancy rates
Ovarian Tissue Cryopreservation (OTC)	
<ul style="list-style-type: none"> • 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 <i>in vitro</i> follicle maturation 	<ul style="list-style-type: none"> • Emerging approach that has resulted in live births
Emerging Technologies for Follicle Maturation	
In Vitro Follicle Maturation	
<ul style="list-style-type: none"> • Mechanism to mature oocytes retrieved from OTC or transvaginal oocyte retrieval • Avoids reimplantation of ovarian tissue • Has resulted in live births 	
Retrievable Hydrogels	
<ul style="list-style-type: none"> • Nascent ovarian follicles encapsulated in hydrogels transplanted in a heterotopic site, allowing <i>in vivo</i> 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	<ul style="list-style-type: none"> - Monitoring: Fetal heart tones before and after surgery - Type: Mastectomy/axillary staging^a recommended
Second	<ul style="list-style-type: none"> - Favorable trimester for non-emergent surgery - Monitoring: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - Intraoperative emergent cesarean delivery is feasible as necessary - Patient has been counseled/consented for cesarean delivery - Type: Mastectomy/axillary staging^a recommended <ul style="list-style-type: none"> - For appropriately selected surgical candidates also being treated with neoadjuvant/adjuvant therapy, can consider lumpectomy with completion of radiation postpartum
Third	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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
Third	
Overall	- Antihormonal therapy contraindicated during all trimesters
	Radiation Therapy
First	<ul style="list-style-type: none"> - Absolutely contraindicated in all trimesters due to fetal toxicity: <ul style="list-style-type: none"> - 1st trimester exposure: Pregnancy loss and congenital malformations - 2nd/3rd trimester exposure: Intrauterine growth restriction, cognitive impairment, fetal death, increased risk of childhood malignancies
Second	
Third	

^aNCCN 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