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ORIGINAL ARTICLE – BREAST ONCOLOGY

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

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ABSTRACT

Background. Breast cancer is the most common malignancy diagnosed in women of childbearing age. A breast cancer diagnosis in this young patient population can be uniquely complex to navigate when considering the potential impact of fertility loss associated with specific gonadotoxic therapies. Another unique challenge for young breast cancer patients is pregnancy-associated breast cancer (PABC), which occurs in approximately 1 of every 3000 pregnancies. Pregnancy adds a layer of complexity to breast cancer treatment planning as many therapies can affect the developing fetus. These two clinical challenges require nuanced multidisciplinary approaches to facilitate optimal treatment outcomes. We sought to review and summarize the management strategy options for both fertility preservation and PABC.

Methods. A guideline and literature review was performed for fertility preservation, young patients with breast cancer, and pregnancy-associated breast cancer.

Results. Fertility preservation options, both established and experimental, are detailed. Suggested clinical practice guidelines for PABC are also presented, which delineate breast cancer treatment recommendations based on pregnancy trimester.

Conclusion. A multidisciplinary approach to patient care, including oncologists and early referral to reproductive specialists, can provide young breast cancer patients with options for fertility preservation. Under the guidance of a multidisciplinary treatment team, PABC can also be diagnosed and treated to permit the best possible outcomes for the mother and the developing fetus.

Annually, invasive breast cancer is diagnosed for 11,160 young women (age < 40 years) in the United States, making it the most common malignancy among women of childbearing age.[1] The management of breast cancer in young patients is associated with unique challenges.[2] Because 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 inability to breastfeed.[4–6] Also, concerns associated with maintaining future fertility can have an impact on a young patient's willingness to undergo recommended cancer treatments.[2,7] Therefore, at the earliest possible time, providers should prioritize a discussion about fertility preservation options before initiation of cancer treatment.[7–10]

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Another challenge associated with the management of young breast cancer patients is pregnancy-associated breast cancer (PABC). Occurring in nearly 1 in 3000 to 10,000 pregnancies, PABC (breast cancer diagnosed during pregnancy or within 1 year postpartum) is most often diagnosed during the postpartum period.[11,12] Because women currently are more frequently delaying childbearing, the incidence of PABC may increase. Although PABC tends to be more advanced at diagnosis, recent studies have shown that outcomes for patients with PABC can be similar to those for nonpregnant patients when matched for tumor characteristics and stage.[3,13,14] Data about the optimal management of PABC continues to evolve, but some guidelines have been established.[10,15,16]

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

IMPLICATIONS OF BREAST CANCER THERAPY FOR FERTILITY

Radiation

The amount of radiation that reaches the ovaries and uterus via scatter during breast/axillary radiation is relatively low. Therefore, 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 because 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% to 60% of women younger than 40 years and in more than 80% of women older than 40 years when these agents are used at higher doses.[6] Anthracyclines are less gonadotoxic than alkylating agents, but still are associated with a high rate of amenorrhea.[22] Taxanes are reported to result in amenorrhea when used in conjunction with anthracyclines and cyclophosphamide.[23,24]

The effect of anti-human epidermal growth factor receptor 2 (HER2)-targeted therapy (e.g., trastuzumab and pertuzumab) has been challenging to assess because these medications often are 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 that any attempts for pregnancy be delayed for at least 7 months after completion of anti-HER2-directed therapy due to risks of teratogenicity.[26]

Endocrine Therapy

Abundant evidence shows 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 of a 10-year tamoxifen treatment duration for many patients.[28] Although tamoxifen treatment has several benefits, this drug also is 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 have been largely reassuring, although generated from retrospective studies.[14] A recent multicenter case–control study by Lambertini et al.[30] found that pregnancy after treatment for breast cancer, regardless of hormone receptor status, did not have an impact on disease-free survival compared with the outcomes for nonpregnant patients. 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 of 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 to 30 months, followed by a 3-month "washout" period before conception. The patients in the study then have a 2-year window to allow for pregnancy and breastfeeding before antihormonal therapy is restarted 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, pregnancy, or both should be undertaken before they pursue invasive fertility preservation options, including oocyte retrieval and oocyte/embryo cryopreservation. Patients desiring future fertility also should 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 sufficiently stable medically 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 before 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 2-week time frame.[38–42] To minimize potential treatment delays, breast cancer

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	Most well-established and successful method of fertility preservation
Concurrent AI therapy can help temper estrogen levels	Live birth rates:
Equivalent live birth rates with frozen embryos (FET) and frozen oocyte-derived embryos transfers (FOET)	FET: 25%
	FOET: 25.1%
Preimplantation genetic diagnosis available for patients with genetic mutations	
GnRH agonist administration	
Concurrent administration with chemotherapy results in lower rate of primary ovarian insufficiency (POI)	Implementation currently considered for ovarian function preservation
Controversy regarding fertility preservation efficacy	Recent data suggest safety and efficacy in preventing POI and increasing pregnancy rates
Recent meta-analysis showed increased pregnancy rate among women who received a GnRH agonist with chemotherapy compared with womens who received chemotherapy alone	
Ovarian tissue cryopreservation (OTC)	
Experimental technique involving surgical excision of ovarian tissue for cryopreservation	Emerging approach that has resulted in live births
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 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 hydrogels transplanted in a heterotopic site, allowing in vivo maturation	
Promising results in murine models	

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, the time to the next cancer treatment did not differ between the patients who underwent COS for fertility preservation and those who elected not to proceed with fertility preservation procedures.[43] Additionally, no differences in the incidence of cancer recurrence or survival were found 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 1166 pg/mL (mean 406.94 ± 256.64 pg/mL or 1486.76 ± 942.13 pmol/L).[44] Currently, no evidence exists to show that the increased circulating estrogen levels associated with COS, with or without letrozole treatment, negatively affect 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 currently is considered equivalent to a fresh oocyte,[49] thereby increasing the preservation options for patients not prepared to preserve embryos. Live birth rates and perinatal outcomes are similar between frozen embryo transfers (25%) and frozen oocyte-derived embryo transfers (25.1%).[50]

Experimental Approaches

GnRH Agonist Administration In the past, the concurrent administration of GnRH agonists (e.g., goserelin, leuprolide, triptorelin) during treatment with chemotherapy has been considered an experimental approach for fertility preservation, 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 who received GnRH agonist therapy than for patients who received chemotherapy alone (14.1% vs 30.9%, respectively; $P = 0.001$).[56] Additionally, the pregnancy rate was significantly higher after treatment for the GnRH agonist therapy group than for the patients treated with chemotherapy alone (10.3% vs 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] The OTC procedure 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 examining studies of ovarian tissue transplantation found a cumulative clinical birth rate of 57.5%.[58] Currently, the potential reseeding of malignant cells with autologous ovarian tissue transplantation is a concern, particularly in the setting of hematologic malignancies and BRCA mutation carriers.[59] Alternatively, in vitro follicle maturation, discussed next, offers another use 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) for later facilitation of IVF.[60] Live births have been attributed to each retrieval method, and data regarding the safety and success of these methods continue to evolve in both the laboratory and clinical settings.[61]

Use of Retrievable Hydrogels Concerns regarding follicular atresia after ovarian transplantation and reseeding of 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. Subsequently, they are transplanted at a heterotopic site in the patient, allowing for in vivo maturation. An early study using a murine model demonstrated survival of multiple follicle populations with minimal evidence of tumor reseeding.[63] This technique continues to evolve and shows promise for premenarchal patients and those unable to undergo COS.

TABLE 2 Major GnRH agonist trials

Trial	GnRH agonist	Outcome (vs controls)
POEMS/SWOG S0230[4]	Goserelin 3.6 mg subcutaneous	Premature ovarian insufficiency: 8% versus 22% ($P = 0.04$) Rates of pregnancy: 21% versus 11% ($P = 0.03$)
Anglo Celtic Group OPTION[107]	Goserelin 3.6 mg subcutaneous	Premature ovarian insufficiency: 18.5% versus 34.8% ($P = 0.048$) Rates of pregnancy: not reported
GBG 37 ZORO[108]	Goserelin 3.6 mg subcutaneous	Resumption of menstruation: 70.0% versus 56.7% ($P = 0.284$)
PROMISE-GIM6[109]	Triptorelin 3.75 mg intramuscular	Premature ovarian insufficiency: 8.9% versus 25.9% ($P = 0.001$)
Munster et al.[110]	Triptorelin 3.75 mg intramuscular	Amenorrhea rates: 88% versus 90% ($P = 0.36$)

Recent major trials assessing the impact of GnRH agonist administration on the rates of premature ovarian insufficiency, resumption of menstruation, and rates of pregnancy

Note All GnRH agonists were administered with the same frequency: 1 week before chemotherapy and every 4 weeks during chemotherapy

Preimplantation Genetic Diagnosis

Reproductive-aged women with a diagnosis of 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, identification of an HBOC mutation can have implications for fertility. If desired by the patient, propagation of the HBOC gene mutation may be prevented by performance of preimplantation genetic diagnosis (PGD) for monogenic diseases based on biopsies from cryopreserved embryos or cryopreserved oocyte-derived embryos.[41] Embryos that do not harbor the HBOC gene mutation then can potentially be selected for implantation.

Although 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, postpartum, and non-pregnant patients. Mammogram and ultrasound both are sensitive and specific during pregnancy.[66,67] With appropriate abdominal shielding, mammography poses minimal risk to the developing fetus.[68] Breast ultrasound is particularly useful because it can distinguish between cystic and solid lesions and is safe during pregnancy.[69] Although gadolinium contrast is considered teratogenic,[67] magnetic resonance imaging (MRI) without gadolinium contrast can help evaluate the breast during pregnancy.[68] No reports have shown harmful effects of MRI on the fetus, and no long-term prospective safety data exist, but MRI should be used with appropriate caution, particularly during the first trimester, when fetal organogenesis occurs.[70] In the postpartum 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 with a diagnosis of breast cancer.[73] Some limited data suggest that the fetal radiation dose is low with 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) only and (18)F-FDG PET/MR, particularly during the later stages of pregnancy, although the existing data are insufficient to establish recommendations regarding the use of PET scanning for cancer staging during pregnancy.[74,75] Radiologists should be involved early in the formulation of the diagnostic strategy to help minimize 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 those for 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

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 and 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 and 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 recommended
Overall	Recommend delaying reconstruction until postpartum period
Systemic therapy	
First	Avoid due to risk of miscarriage and fetal congenital malformations
Second	Chemotherapy generally considered safe without long-term complications
Third	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 to 37 weeks to minimize hematologic toxicity
Overall	Antihormonal therapy contraindicated during all trimesters
Radiation therapy	
First	Absolutely contraindicated in all trimesters due to fetal toxicity:
Second	First trimester exposure: pregnancy loss and congenital malformations
Third	Second and third trimester exposure: intrauterine growth restriction, cognitive impairment, fetal death, increased risk of childhood malignancies

HER2, human epidermal growth factor receptor 2

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines offer management recommendations based on breast cancer subtype.[10] Given the nuanced care required for the management of both breast cancer and pregnancy, we advocate for the organization of treatment recommendations by pregnancy trimester. Importantly, treatment decisions must be agreed upon collaboratively by the patient and the treatment team; including oncologists and obstetric providers

[a]The National Comprehensive Cancer Network (NCCN) Guidelines state that axillary staging can be performed using axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) with technetium 99 m 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]

has an impact on treatment options and sequencing of therapies (Table 3).

Treatment Options and Pregnancy

Surgery Surgery can be performed during any trimester of pregnancy, although the 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 (before 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 for 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 in which chemotherapy also is 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 with a diagnosis determined in the third trimester for whom radiation therapy can be safely initiated after delivery.[15]

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

The NCCN guidelines state that axillary staging may be accomplished safely during pregnancy with a sentinel lymph node biopsy (SLNB) an axillary lymph node dissection (ALND), or both, but decisions should be made on a patient-to-patient basis.[15] Han et al.[81] showed the safety of SLNB for pregnant patients, with an axillary recurrence rate comparable with that for non-pregnant patients. 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 durng 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 also is associated with pregnancy loss and congenital malformations.[88] The current recommendations are to delay radiation therapy until the postpartum period.

Lactation is possible after breast radiation therapy. A literature review showed that approximately 50% of patients who 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 after 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 trimesters increases the 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 before delivery.

Most chemotherapy safety data are 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] Some data from case reports suggest that taxanes may be safe for use during pregnancy.[98,101,102] However, the 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 antiemetics 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 also has been reported,[103] although it 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 also is 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, because many systemic agents are cytotoxic, breastfeeding during treatment with systemic therapy is not recommended.[91]

SUMMARY

The management of breast cancer in reproductive-age women is associated with unique complexity compared with 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 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. Although 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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