

Breast cancer and pregnancy: Why special considerations prior to treatment are needed in multidisciplinary care

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SUMMARY Breast cancer diagnosed during pregnancy poses ethical and professional challenges. Clinical management of that condition should ensure the safety of both the mother and fetus. Clinical trials on breast cancer exclude pregnant women, so sufficient evidence with which to formulate guidelines for the management of these patients is lacking. Failing to undergo a breast examination during pregnancy, breast symptoms explained by physiological changes such as pregnancy, and unnecessary abortions after the diagnosis of breast cancer lead to worse outcomes for these patients. Multidisciplinary teams including breast surgeons, obstetricians, radiologists, pathologists, and anesthesiologists need to make an early diagnosis and comprehensively evaluate patients in different gestational weeks and with different stages of breast cancer in order to optimize outcomes.

Keywords breast cancer diagnosed during pregnancy, multidisciplinary teams, special considerations

1. Introduction

Breast cancer (BC) is the most common carcinoma in women worldwide (1-5), and about 7% of the cases were diagnosed before the age of 40 years (6,7). Cancer diagnosed during pregnancy is rare, with an incidence of 1 case per 1,000 deliveries (8). Breast cancer developing during pregnancy is rare, but it is the most common cancer affecting pregnancy. The incidence of breast cancer during pregnancy has been increasing (9). The rate of breast cancer among pregnant women age < 45 years has varied from 2.6% to 6.9% (10). By comparison, the rate in those age < 35 years has been 15.6% for all breast cancer cases (11).

BC diagnosed during pregnancy presents a complex challenge to the patient and to clinicians deciding how to manage the condition. Although the expectations are that pregnant patients with breast cancer will be treated as effectively as nonpregnant patients with breast cancer, the selection and delivery of standard therapies must be modified to balance maternal benefit and fetal risk. Assessment of the risks and benefits and a multidisciplinary team (MDT) approach at specialized centers are crucial to managing this group of patients (12-16).

The aims of the current article are to highlight the special considerations for pregnant women prior to

treatment of breast cancer (Table 1) and to review the evidence for management of pregnant patients with breast cancer.

2. Tumor biology

Although the clinical characteristics of breast cancer in pregnant women are similar to those in non-pregnant women, diagnosis may be delayed due to the differential diagnoses of physiologic alterations related to pregnancy (17,18). Breast cancer is not caused by pregnancy but can occur coincidentally with pregnancy. Pregnancy may have a profound effect on the biology of breast cancer. Most of the breast cancer developing during pregnancy is invasive ductal carcinoma (19). Invasive lobular carcinoma develops far less frequently (20). Studies have reported that triple-negative breast cancer (TNBC) is more prevalent during pregnancy (21-23). The ultimate prognosis for breast cancer during pregnancy is a subject of debate. Although some studies have noted no significant differences in the prognosis for breast cancer during pregnancy or otherwise (24-26), a recent meta-analysis noted a poor prognosis for breast cancer in pregnant women (27). Compared to sporadic breast cancer, breast cancer that develops during pregnancy has a higher histologic grade, a more aggressive profile, is in a more advanced stage at

Table 1. Special considerations when managing pregnant women with breast cancer

At diagnosis

- Calculate the gestational age and expected date of delivery
- Conduct a standard staging workup
- Complete a fetal examination before treatment

During pregnancy

Surgery

- Radical modified mastectomy or breast-conserving surgery is recommended for early-stage breast cancer

Systemic Treatment

- Chemotherapy is safe in the second and third trimesters
- AC (doxorubicin and cyclophosphamide) and EC (epirubicin and cyclophosphamide) are the most frequently used regimens

Delivery

- The mode of delivery is decided by obstetric indications
- Chemotherapy should not be administered after 35 weeks of gestation

Diagnostic tests	First trimester	Second trimester	Third trimester
Breast ultrasound	Green	Green	Green
Noncontrast breast MRI	Green	Green	Green
Mammography	Yellow	Yellow	Yellow
Chest radiography	Yellow	Yellow	Yellow
Liver ultrasound	Green	Green	Green
Bone scans and PET	Red	Red	Red
Noncontrast skeletal MRI	Green	Green	Green

■ recommended
■ only in selected cases
■ contraindicated

Figure 1. Management of tests to diagnose breast cancer during pregnancy per trimester. MRI magnetic resonance imaging, PET positron emission tomography. Green: recommended; Yellow: only in selected cases; Red: contraindicated.

diagnosis, is larger in size, has a higher frequency of nodal involvement, less frequently expresses estrogen receptors (ERs) and progesterone receptors (PRs), and is more likely to be inflammatory breast cancer (28).

The effects of pregnancy may alter certain patterns of gene expression in breast cancer cells compared to normal breast tissue (29,30). The aberrant expression of several oncogenes (*MYC*, *SRC*, and *FOS*), tumor suppressor genes (*TP53*, *PTEN*, and *CAVI*), apoptosis regulators (*PDCD4*, *BCL2*, and *BIRC5*), transcription regulators (*JUN*, *KLF1*, and *SP110*), genes involved in DNA repair mechanisms (*Sig20*, *BRCA1*, *BRCA2*, and *FEN1*), genes involved in cell proliferation (*AURKA* and *MKI67*), genes involved in the immune response (*PDI* and *PDL1*), and genes involved in other significant biological processes (protein modification or internal cell motility) has been noted in breast cancer diagnosed during pregnancy (29).

3. Diagnosis and staging

Diagnostic tests to diagnose breast cancer during pregnancy per trimester are summarized in Figure 1.

During pregnancy, the diagnosis of breast cancer is often delayed about 1 to 13 months due to enlargement of the breasts, colostrum secretion, and other changes (31). Although 80% of palpable breast masses found during pregnancy are benign, a mass diagnosed for > 2

weeks should be taken seriously (32).

The workup of a suspicious breast mass proceeds similarly during pregnancy or otherwise, but the standard staging workup should be predicated on fetal safety. A careful physical examination for suspected breast cancer during pregnancy that includes the breasts and regional lymph nodes is essential. A point worth noting is that breast ultrasonography should be the first imaging technique used to assess a breast mass during pregnancy because of its safety and high level of sensitivity. Although breast ultrasonography is less sensitive due to a higher density of the breast during pregnancy, mammography with appropriate abdominal shielding should be useful at evaluating the extent of disease (33,34). Gadolinium can cross the placental barrier and is considered potentially teratogenic (35), so magnetic resonance imaging (MRI) without gadolinium contrast can be used to further evaluate the breast during pregnancy (33).

A histopathologic examination of core needle biopsy specimens obtained under local anesthesia is the preferred method of sampling any clinically suspicious breast mass during pregnancy or otherwise (13). Suspected metastatic lymph nodes should also be evaluated with ultrasound and fine needle aspiration biopsy for cytologic confirmation (36). Pathologists should be informed of the patient's pregnancy because the presence of hyperplastic cells could simulate atypia,

leading to an increase in false-positive results (37).

Systemic staging studies are recommended for advanced cancers. Staging studies on patients during pregnancy must be performed only if the treatment options are going to be adjusted. If necessary, staging tests should include chest radiography with abdominal shielding, liver ultrasonography, and/or noncontrast skeletal MRI. The ESMO guidelines point out that bone scans and positron emission tomography (PET) should be avoided during pregnancy (38). Although a few studies have indicated that fluorodeoxyglucose (18F-FDG) PET and PET/magnetic resonance imaging (MRI) involve a low dose of fetal radiation exposure, there is not enough evidence to support the use of PET for breast cancer staging during pregnancy (39,40). Contrast-enhanced CT should be avoided during pregnancy.

A radiologist needs to be a key member of the medical team in order to calculate the total dose and review the indications as well as their risk-benefit ratios (41).

4. Pregnancy monitoring

Pregnant women with breast cancer should always be considered a high-risk group. Therefore, more careful and continuous monitoring with morphometric ultrasonography and umbilical artery Doppler assessment during gestation is mandatory. Calculation of gestational age and expected date of delivery are significant, which has an impact on breast cancer treatment planning (42,43). Allowing a pregnancy to reach full term (37 weeks) is strongly recommended. The gynecologist/obstetrician should be the part of the multidisciplinary team and determine the mode of delivery (44). Possible micrometastases in the placenta should be examined. In order to avoid hematological toxicity in the mother and fetus, the management of the last round of chemotherapy should be 3 weeks prior to the planned date of delivery (3). There is mounting evidence regarding the effects of breast cancer treatment on pregnancy outcomes. In general, therapy for breast cancer during pregnancy had no clear adverse effects on growth, cognitive function, and cardiac function in early childhood, suggesting that the diagnosis of cancer during pregnancy should not be an indication to abort the pregnancy. The only factor associated with a worse cognitive outcome was prematurity, irrespective of anticancer treatments (45).

5. Risk of anesthesia

Anesthesia considerations also include the safety of both the mother and the fetus. Changes in maternal anatomy and physiology during pregnancy increase the potential hazards for the mother and fetus undergoing anesthesia. Maternal changes include increased cardiac output (46), reduced functional residual capacity (47), dilation of the pyelocaliceal system (48), dilutional

anemia (49), gastroesophageal reflux (50), and changes in glucose and adrenal metabolism (51). The risk of anesthesia-related morbidity and mortality during pregnancy mostly involves airway edema, restrictive lung physiology, and aspiration (52). A previous study suggested that adverse fetal outcomes after surgery may contribute to the mother's underlying condition rather than the effects of anesthesia (53). A point worth mentioning is that the patient should be positioned with a 15-30° left lateral tilt in order to reduce aortocaval compression and the incidence of supine hypotensive syndrome (54).

6. Treatment

Guidelines state that breast cancer during pregnancy should be treated in accordance with the management of breast tumors in non-pregnant women, including the local control of disease and the prevention of systemic metastases (38,39). To optimize the management of breast cancer during pregnancy, clinicopathological characteristics, gestational age at the diagnosis of breast cancer, expected date of delivery, and the patient's wishes should be considered. The goals of the multidisciplinary team are to cure the pregnant patient with breast cancer, to support the pregnancy, and to not harm the fetus (12).

6.1. Surgery during pregnancy

Surgery can be considered safe in all trimesters of pregnancy (38). The gestational age at diagnosis is an important factor in devising a surgical plan. Either a radical modified mastectomy (RMM) or breast-conserving surgery is a reasonable option for a pregnant woman with breast cancer. In the first trimester, however, radiotherapy following breast-conserving treatment may be delayed for the sake of fetal safety. Mastectomy should be recommended for patients who wish to continue the pregnancy (55). Breast-conserving surgery might be an option for early-stage BC in the second and third trimesters. Reconstructive surgery should be postponed until after birth, given concerns about normal changes in the breast after pregnancy and its unexpected cosmetic effects (56).

Although breast cancer during pregnancy has a high incidence of axillary metastases, sentinel lymph node biopsy should be suggested for patients with early-stage breast cancer. There is no level I evidence to support sentinel lymph node biopsy for breast cancer patients during pregnancy. The American Society of Clinical Oncology (ASCO) guidelines do not support this procedure (57). The National Comprehensive Cancer Network (NCCN) guidelines endorse the safety of this approach pursuant to the patient's wishes (57,58). Other guidelines advise sentinel lymph node biopsy when axillary ultrasound and a suspicious lymph node biopsy

are negative (59).

A sentinel lymph node biopsy should be performed using ^{99m}Tc -albumin nanocolloids (39). Blue dye and isosulfan blue should be avoided because of the risk of an allergic or anaphylactic maternal reaction, and methylene blue is contraindicated during the first trimester because it is teratogenic (60).

6.2. Systemic treatment during pregnancy

Generally, systemic treatments including chemotherapy, hormone therapy, targeted therapies, and immunotherapy are avoided in the first trimester because of the high risk of teratogenicity and abortion (Figure 2) (39,61,62). Available data on the teratogenic risks to pregnant women from all clinical trials are limited to case reports, animal studies, and studies with small samples. The major factors that should be taken into account before systemic therapy during pregnancy include physiologic changes during pregnancy, gestational age, placental passage, and the pharmacokinetic characteristics of the drug. Before any oncological treatment, a fetal ultrasound must be performed to exclude pre-existing abnormalities (60).

Anthracyclines are considered the treatment of choice because of the very low placental transfer (63). A previous study has reported that doxorubicin and epirubicin are not teratogenic (64), but another study reported that they tend to cause prematurity and low birth weight (65). Retrospective and prospective studies have examined different schedules and chemotherapy combinations, such as 3-week cycles of FAC (5-fluororacil, doxorubicin, and cyclophosphamide), FEC (5-fluororacil, epirubicin, and cyclophosphamide), AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide), or weekly epirubicin as monotherapy (62,64-66). The AC and EC regimens are most often used to treat breast cancer during pregnancy. A retrospective cohort study indicated that dose-dense chemotherapy was safe in 10 pregnant women with breast cancer (67). However, a dose-dense schedule may not be recommended (68). Although chemotherapy has considered safe and well-tolerated, the multidisciplinary team must monitor fetal safety and maternal blood pressure. Moreover, chemotherapy should not be

administered after 35 weeks of gestation in order to prevent hematological complications during delivery (69,70).

The use of trastuzumab throughout pregnancy is contraindicated due to the high risk of oligohydramnios and/or anhydramnios (39). The *erbB2/neu* gene is related to fetal organogenesis (71). A systematic review and meta-analysis of the safety of trastuzumab during pregnancy concluded that more adverse events occur during the second/third trimester than during the first trimester (72). No data are available on pertuzumab and *T-DMI* administration in pregnant women, so both are contraindicated (73). A small molecule, lapatinib is presumed to be able to cross the placenta during all phases of pregnancy. The limited data on use of this tyrosine kinase inhibitor during pregnancy do not support its use in pregnant patients (74,75). Data on the use of *CDK4* and *CDK6* inhibitors throughout pregnancy are not yet available.

Endocrine therapy (tamoxifen and luteinizing hormone-releasing hormone analogues) is contraindicated for the treatment of breast cancer during pregnancy due to the high risk of birth defects (up to 17.6%) (76). Tamoxifen is teratogenic and increases the risk of breast cancer in offspring which has been verified in animal experiments (77,78). A systematic review has summarized major malformations (ambiguous genitalia, Pierre Robin sequence, and oculoauriculovertebral dysplasia) and minor malformations (preauricular skin tags and severe hypermetropia) in breast cancer patients exposed to tamoxifen during pregnancy (79). No data are available on human exposure to aromatase inhibitors during pregnancy, though there are data from animal models (80).

Radiation has dose- and gestational-week-dependent effects on the fetus (81). Due to its teratogenic effects, radiation therapy is not considered a safe treatment option (82). Radiotherapy could be performed in the first trimester and at the beginning of the second after a careful dose adjustment (exposure of 0.01 mGy is below the threshold dose) and proper abdominal shielding (83). The multidisciplinary team should balance the risks and benefits of administering radiotherapy, both for the mother and the fetus.

The *PD-1/PD-L1* pathway is involved in immune

System Treatment	First trimester	Second trimester	Third trimester
Chemotherapy	Red	Green	Green
Radiotherapy	Yellow	Red	Red
Endocrine therapy	Red	Red	Red
Targeted therapy	Red	Red	Red
Immunotherapy	Red	Red	Red

■ recommended
■ only in selected cases
■ contraindicated

Figure 2. Systemic treatment per trimester. Green: recommended; Yellow: only in selected cases; Red: contraindicated.

tolerance during pregnancy (84). In models involving pregnant animals, anti-*PD-1/PD-L1* treatment increased the risk of miscarriages, premature delivery, and birth mortality (85), so immunotherapy during pregnancy is contraindicated.

7. Conclusion

The management of breast cancer during pregnancy is a major ethical and professional challenge for both the patient and the multidisciplinary treatment team. Due to the special physiological stage that those patients are in, some special considerations should be made. The patient's medical history needs to be understood in detail, the patient needs to be evaluated as comprehensively as possible *via* limited additional examinations, and the entire pregnancy should be monitored in order to formulate a reasonable treatment plan, to ensure the safety of the fetus and the mother, and to ensure the effectiveness of cancer treatment.

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