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Pregnancy-Associated Breast Cancer: A Literature Review

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Breast cancer, along with cervical cancer, is one of the most commonly diagnosed cancers of pregnancy. Most would define gestational breast cancer as breast cancer that is diagnosed during pregnancy, lactation, and up to 12 months post-partum. The diagnostic and therapeutic implications in this clinical setting are special. These women typically present with a more advanced-stage disease that carries an associated poorer prognosis. Physicians thus are challenged to balance aggressive maternal care with appropriate modifications that will ensure fetal protection.

Epidemiology

Based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Program Cancer Statistics Review and rates from 2001 to 2003, 12.67% of women will develop breast cancer during their lifetime. This lifetime risk translates into one in eight women. Additionally, this review notes that the mean age at diagnosis for breast cancer from 2000 to 2003 was 61 years, and only approximately 12.7% of women were between the ages of 20 and 44 [1]. Of women diagnosed with breast cancer younger than 40 years, only approximately 10% will be pregnant [2,3]. These data certainly suggest a low incidence of pregnancy-associated breast cancer. In fact, historically, the incidence is estimated at 1 in 3000 pregnancies [4–6]. Despite the overall low incidence, however, gestational breast cancer is one of the most common pregnancy-associated malignancies, second only to cervical cancer [4,6]. Notably, many have offered that this incidence will only increase as more women delay childbearing until later in life [4,7]. This concern is based on the fact that pregnancy-associated breast cancer is age-related, and women

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who have their first term pregnancy after the age of 30 years have a two to three times higher risk of developing breast carcinoma than women who have their first pregnancy before the age of 20 years [8]. Presently, most studies support a mean age at diagnosis of 32 to 34 years [8–11].

Prognosis

Clinical staging of these patients does not waver from the TNM staging system of the American Joint Committee on Cancer. Historically pregnancy-associated breast cancer was thought to be rapid in course, excessively malignant, and incurable [12,13]. More recently, the prognosis of gestational breast cancer has been shown to be similar to that of nonpregnant women when age and stage at presentation are accounted for (Table 1) [4,14,15]. Notably, both Anderson and colleagues [16] and Ishida and colleagues [9] document no difference in the prognosis of early cancers (when matched for age and stage), but a poorer prognosis is demonstrated for patients with more advanced disease. Numerous studies have documented that these women present with larger tumors and have a higher incidence of lymph node metastases (56% to 89% when compared with 38% to 54% in nonpregnant young women) that appears to translate into a more advanced stage [7–9,17–21]. Most women present with stage II or III disease (65% to 90% compared with 45% to 66% of nonpregnant controls) [8,9,17].

Table 2 references the 5- and 10-year survival for node-negative and node-positive disease for pregnancy-associated breast cancer as 60% to 100% and 31% to 52% respectively [7,22,23]. A delay in diagnosis, on the part of physician and patient alike, is thought to contribute to the advanced disease at presentation. This in part, is attributed to the engorgement and physiologic hypertrophy of the pregnant or lactating breast. It is no longer accepted that pregnancy is an independent risk factor for poor prognosis, and there is no clear evidence to support that the hyperestrogenic state of pregnancy contributes to development and rapid growth [24].

Pathology

Table 3 references the general pathology of pregnancy-associated breast cancer. Invasive ductal carcinoma predominates. As mentioned previously, these tumors are typically larger in size at presentation. Additionally, there is a higher frequency of lymphovascular invasion, high nuclear grade, and hormone independence. These histopathologic and immunohistochemical features are similar to those of nonpregnant young women with breast cancer, and they are felt to be determined by the age of diagnosis rather than pregnancy [4,25,26].

The degree of hormone receptor status negativity is consistently greater in the pregnant cohort of young women diagnosed with breast cancer. Several theories persist. The first is that the high circulating levels of

Table 1
Selected studies comparing prognosis of patients with gestational- and nongestational breast cancer controls

Author/date	Number of patients (GBC versus non-GBC)	Survival type	Subgroup	Survival rate (GBC) %	Survival rate (non-GBC) %
Nugent and O'Connell/ 1985 [2]	19 versus 157	5-year survival		57	56
Ishida et al/1992 [9]	192 versus 191	10-year survival	All	55	79
			Node-negative	85	93
			Node-positive	37	62
Zemlickis et al/1992 [14]	118 versus 269	10-year survival	All	40	48
Petrek/1994 [19]	22 versus 103	5-year survival	Node-negative	82	82
	47 versus 63		Node-positive	47	59
Anderson et al/1996 [16]	22 versus 205	10-year survival	Stage I-IIA	73	74
			Stage IIB-IIIA	17	47
Ezzat et al/1996 [15]	37 versus 84	7-year survival (overall)	All	57	61
		7-year survival (relapse-free)	All	37	33
Bonnier et al/1997 [27]	154 versus 308	5-year survival (metastases-free)	All	45	68
		5-year survival (recurrent-free)	Node-negative	63	77
			Node-positive	31	63
			All	69	81
		5-year overall survival	All	61	75

Abbreviation: GBC, gestational breast cancer.

Data from Loibl S, von Minckwitz G, Gwyn K, et al. Breast cancer during pregnancy—international recommendations from an expert meeting. Cancer 2005;106(2):237–46.

Table 2
Selected studies comparing 5-year survival rates, considering nodal status

Author/date	Node-negative (n)	Node-positive (n)
King et al/1985 [22]	82% (22)	36% (36)
Nugent and O'Connell/1985 [2]	100% (4)	50% (15)
Petrek et al/1991 [18]	82% (22)	47% (34)
Ishida et al/1992 [9]	90% (71)	52% (101)
Kuerer et al/1997 [23]	60% (14)	45% (12)
Bonnier et al/1997 [27]	63% (50)	31% (64)
Reed et al/2003 [17]	62% (31)	40% (69)

n = sample size.

estrogen and progesterone in pregnancy may occupy all of the hormone receptor binding sites; the second relates to receptor down-regulation during pregnancy [7,9,27,28].

Additionally, a retrospective and multi-institutional study from Bonnier and colleagues [27] found immunohistochemical assessment of hormone receptor status to be more reliable than a ligand-based assay. Ligand-based assays depend upon the availability of unbound hormone receptors, which may be less accurate during pregnancy secondary to interference by circulating steroid receptors. Finally, there is no consensus regarding the prevalence or implication of HER-2/neu overexpression in pregnancy-associated breast cancer.

Diagnostic evaluation

Most women diagnosed with pregnancy-associated breast cancer will present with a painless mass in the breast. A milk-rejection sign has been described rarely in case reports when a nursing infant refuses a lactating breast that harbors occult carcinoma [29,30]. The differential diagnosis of a pregnancy-associated breast mass is broad and includes:

Invasive carcinoma
Lactating adenoma
Fibroadenoma
Cystic disease
Lobular hyperplasia
Milk retention cyst (galactocele)
Abscess
Lipoma
Hamartoma and rarely leukemia
Lymphoma
Sarcoma
Neuroma
Tuberculosis [31]

Table 3
Selected studies examining pathologic features of pregnancy-associated breast cancer

Author/date	N	Histology	Histo–prognostic grade	ER (+) %	PR (+) %	Assay	Her-2/neu (+) %
Elledge et al/1993 [28]	15 (versus 411 NPCs)	N.E.	N.E.	33 (versus 52% in control group) 50 (n = 12)	47 (versus 43% in control group) 83 (n = 10)	LBA IHC	58 (versus 16 in control group)
Ishida et al/1992 [9]	192 (versus 411 NPCs)	92.1% IDC 1.6% in situ 1.6% mucinous 3.7% med	N.E.	44 (versus 57% in control group)	29 (versus 69 in control group)	LBA	N.E.
Bonnier et al/1997 [27]	154 (v. 308 NPCs)	88.2% IDC 8.2% ILC 2.7% med	12% I 48% II 40% III	45 (versus 63.7 in control group) 46.7 (versus 53.9)	46.2 (versus 75.7 in control group) 34.2 (versus 65.8)	LBA IHC	N.E.
Shousha/ 2000 [25]	14 (versus 13 NPCs)	71% IDC 7% ILC 7% in situ 14% mucinous	0% I 20% II 80% III	50 (versus 91 in control group)	30 (versus 64 in control group)	LBA	44 (versus 18 in control group)
Middleton/ 2003 [8]	39	100% IDC	84% poorly differentiated	28	24	IHC	28
Reed et al/ 2003 [17]	122	85% IDC 2.4% ILC 4% In Situ	4% I 37.7% II 48.3% III	31.5 (versus 44% in control group)	22.5 (versus 42% in control group)	IHC	40.5% (versus 28% in control group)
Gentilini et al/2005 [26]	38	95% IDC	N.E.	24 ER or PR+ 36.8 ER and PR+		IHC	21
Ives et al/ 2005 [10]	148	85% IDC 4.7% ILC 2.1% in situ	2.8% I 15.9% II 44.8% III	35.1	N.E.	Unknown	N.E.
Hahn et al/ 2006 [11]	57	85% IDC	16% II 82% III	31 (n = 36)	17 (n = 35)	IHC	29
Yang et al/ 2006 [33]	23	78% IDC	17% mod diff 63% poor diff	27 (n = 15)	13 (n = 15)	Unknown	36% (n = 14)

Abbreviations: diff, differentiated; IDC, invasive ductal carcinoma; IHC, immunohistochemical examination; ILC, invasive lobular carcinoma; LBA, ligand-based assay; med, medullary carcinoma; mod, moderately; N, number of subjects; N.E., not examined; NPCs, nonpregnant controls.

Although 80% of these masses are benign, further evaluation is warranted if findings persist more than 2 to 4 weeks [7,32]. Evaluation begins with a thorough clinical examination, and a baseline breast examination is recommended at the first prenatal visit [4].

Mammography in young nonpregnant and nonlactating women (<35 years) often reveals dense breast parenchyma, contributing to the recommendation that mammography should not be employed for routine screening purposes in this patient population. As breast size and parenchymal density increase during pregnancy and lactation secondary to hyperestrogenic proliferative changes, the corresponding efficacy of mammography historically has been questioned [7]. More recently, both the safety and efficacy of mammography during pregnancy have been supported, and mammographic sensitivity rates of 78% to 90% have been documented [33–36]. A retrospective review by Yang and colleagues [33] of 20 pregnant patients imaged during pregnancy preoperatively found mammography to be 90% sensitive in detecting suspicious features of malignancy. Importantly, 33% of these tumors exhibited secondary features of malignancy, considered to be more subtle (ie, increased breast density and architectural distortion) and felt to contribute to the false-negative rate associated with mammography during pregnancy [33]. Regarding the risk of fetal irradiation, with proper abdominal shielding, the estimated fetal dose of radiation from a standard two-view mammogram (200 to 400 mrad) is less than 0.004 Gy [7]. This is negligible and well below the threshold exposure of the 100 mGy that is associated with a 1% risk of fetal malformation and central nervous system problems as published by the International Commission of Radiological Protection [37].

Ultrasound offers an excellent adjuvant role in the early work-up of a breast mass with no risk of fetal irradiation. The same study by Yahg and colleagues noted ultrasound to be 100% sensitive in detecting a breast mass correlating with a palpable abnormality, supporting previously published data [33,35,36]. Additionally, ultrasound detected additional tumors in the breast in 20% of patients in this same series, and detected axillary metastases in 83% of those imaged (supported by US-guided fine needle aspiration [FNA]) [33]. It appears to be complimentary for staging and detecting mammographic false-negative disease, and it may aid in the assessment of response to neoadjuvant therapy [33].

Further acceptable imaging modalities for staging, as clinically indicated, include chest radiograph with abdominal shielding (fetal irradiation exposure <0.01 mGy), abdominal ultrasound or MRI and thoracic/lumbar MRI. As Gandolinium crosses the placenta and is associated with fetal abnormalities in rats (Category C), contrast-enhanced MRI is not recommended [4,7,37]. A routine bone scan results in 4.7 to 1.8 mGy of fetal exposure, which varies with gestational age; this is not recommended during pregnancy [4,37].

Despite negative findings on breast imaging, pathologic diagnosis with biopsy is recommended for persistent masses, as with breast cancer in general.

FNA, core needle biopsy, and excisional biopsy are all reasonable modalities. Historically pregnancy-related hyperplastic changes with atypia were thought to result in false-positive FNA results; however, several authors have demonstrated marked accuracy and a reduction in surgical biopsy rates when performed by a skilled pathologist made aware of the patient's pregnant or lactating state [38–41]. Core needle and excisional biopsy may be employed also. There are only case reports to support the frequency of milk fistula as a complication, and this may be reduced by emptying the breast of milk before biopsy with ice packs, breast binding, and bromocriptine [7,42].

Management

There is no longer a role for therapeutic abortion. The therapeutic approach to pregnancy-associated breast cancer is similar to that in nonpregnant women: to achieve local control of disease and prevent systemic metastases. Treatment guidelines for nonpregnant patients are followed, allowing for fetal-protective modifications. Each patient's approach must be individualized, taking into account gestational age at presentation, patient's stage of disease, and patient preference [4]. A multidisciplinary approach should be embraced, allowing for close coordination between medical oncology, surgical oncology, and high-risk obstetrics. Genetic counseling is recommended for all women. The need for psychological support is emphasized.

Surgery

The safety of surgical intervention during pregnancy is well supported, but it may be deferred until the 12th gestational week given that the risk of spontaneous abortion is greatest during the first trimester [7,11,24,43,44]. Historically, a modified radical mastectomy was considered the standard of care for all resectable disease during each trimester. This approach both eliminates the need for breast irradiation and definitively manages the axilla. Breast conservation therapy (BCT) increasingly is offered to these young women, although limited by the risks of fetal irradiation postoperatively. Although lumpectomy is considered safe during all trimesters, the required postoperative therapeutic irradiation necessary to complete BCT and obtain optimal local control is considered contraindicated during all trimesters. Appropriate candidates for BCT include women diagnosed late in the second trimester or third trimester so that radiation therapy may be deferred until after delivery, and those women with advanced-stage disease in which neoadjuvant therapy may acceptably delay definitive local resection [4].

Irradiation

Fetal radiation risks are most significant during the first trimester (before the completion of organogenesis) and least during the third trimester. Risks

include teratogenicity, spontaneous abortion and childhood neoplasia, and hematologic disorders. During weeks 2 to 8, during organogenesis, fetal malformations may arise with exposure to a threshold dose greater than 100 to 200 mGy [37,45]. During weeks 8 to 25, the central nervous system is especially sensitive to radiation, and exposure to a threshold dose of 0.1 to 0.2 Gy may decrease the intelligent quotient (IQ), while fetal exposure to 1 Gy increases the probability of severe mental retardation [37,45]. Additionally, fetal exposure to 0.01 Gy increases the incidence of spontaneous childhood cancer and leukemia by 40% (over a background risk of three to four per 1000) [37,45].

The typical dose for therapeutic breast or chest wall irradiation is 50 Gy; this results in fetal exposure of 0.05 to 0.15 Gy and up to 2 Gy toward the end of gestation as the fetus lies closer to the irradiated field in position [45–47]. Notably, there have been case reports of normal infants born to irradiated mothers and successful radiation therapy for Hodgkin disease during pregnancy with appropriate supplemental shielding [32,45,47–49]. Additionally, the 2006 international recommendations from an expert meeting published by Loibl and colleagues [4] regarding therapeutic irradiation have recently been challenged by authors who feel the risks of fetal irradiation exposure have been overestimated [49]. These authors present that the fetal dose caused by leakage radiation from the tube head of the linear accelerator and scatter from collimator and blocks can be reduced with a factor two to four by proper shielding, thereby keeping the radiation dose below the threshold dose for deterministic effects in most cases [49].

Management of the axilla

Appropriate interrogation and management of the axilla are necessary to ensure correct staging at the time of presentation and to drive the appropriate definitive therapy. As mentioned previously, these women present with an increased frequency of nodal involvement. Notably, the early diagnosis of axillary metastases may increase patient stage such that she becomes an acceptable candidate for neoadjuvant chemotherapy, thereby allowing for BCT [4]. Certainly, axillary ultrasound with sonographic-guided FNA of suspicious nodes may be helpful in diagnosing metastatic disease [33]. Currently, axillary lymph node dissection remains the standard of care for these women.

Intraoperative lymph node mapping and sentinel lymph node biopsy remain controversial for two reasons. First, Isosulfan blue dye is classified as a pregnancy category C drug and subsequently is not recommended in these patients. The sensitivity of sentinel lymph node biopsy is reduced when using only the radiocolloid to guide mapping [4]. Second, there are justifiable concerns regarding the risk of fetal irradiation with the use of a radiocolloid in pregnancy, specifically ^{99m}Tc-Sulfur Colloid [50,51].

Nicklas and Baker suggested that sentinel lymph node biopsy might be safe during pregnancy with a minimal dose of 500 to 600 μCi using double-filtered ^{99m}Tc-Sulfur Colloid [7,51]. Several publications have followed to support that fetal radiation exposure from this procedure is actually quite minimal and that sentinel lymph node biopsy may serve more of a role during pregnancy. Using two nonpregnant patient exposures, Keleher and colleagues [52] in 2004 estimated the maximum absorbed dose to the fetus/embryo in pregnant women undergoing breast lymphoscintigraphy with 92.5MBq (2.5mCi) of ^{99m}Tc-Sulfur Colloid as 4.3 mGy using the Medical Internal Radiation Dosimetry (MIRD) program. The same year, Gentilini and colleagues [53] measured activity using thermoluminescent dosimeters combined with static and whole-body scintigraphic imaging in 26 nonpregnant patients exposed to lymphoscintigraphy and overestimated the fetal absorbed dose as 61 μGy. In 2006, Pandit-Taskar and colleagues [54] retrospectively assessed the absorbed doses to various organs and a modeled fetus using standard internal absorbed dose assessment methodologies and phantom models in 1021 nonpregnant women undergoing sentinel node mapping and biopsy and estimated the absorbed fetal dose as 14 μGy. Finally, also in 2006, Mondi and colleagues [50] reviewed one institution's experience with sentinel node mapping and biopsy during pregnancy for breast cancer and melanoma. Although limited ($n = 9$), the review noted no adverse reactions to the procedure itself; all pregnancies were delivered at term. Additionally, there have been no birth defects or discernable malformations.

It is unclear whether the lymphatic drainage of the breast is altered by pregnancy, but there is no evidence to support this [50,55]. Additionally, sentinel lymph node biopsy in pregnancy has not been evaluated systematically. The estimated fetal absorbed dose of radiation, however, is negligible, and recent recommendations from an international expert panel meeting in 2006 suggest that pregnant patient could be offered sentinel lymph node biopsy after extensive counseling regarding the amount of radiation involved, the overall safety, and efficacy [4].

Systemic therapy

Chemotherapy serves an important role in adjuvant and neoadjuvant therapy for patients who have pregnancy-associated breast cancer, especially as so many will present with advanced-stage disease. Although all chemotherapy agents used in the treatment of breast cancer in pregnancy are Category D (ie, teratogenic effects have occurred in people), a surprising safety profile has been demonstrated if administered outside of the first trimester [4,7,11,56–62]. Most frequently documented complications included preterm delivery, low birth weight, transient leukopenia of the newborn, and intrauterine growth restriction. Doll and colleagues [59] in 1989 note that the incidence of fetal malformations with first-trimester chemotherapy

with various agents ranged from 14% to 19%. This value compared with the 1.3% incidence of fetal malformations associated with chemotherapy administered in the second and third trimesters.

The largest prospective series of pregnancy-associated breast cancer treated with cytotoxic chemotherapy in the second and third trimesters initially included 24 women and came from the University of Texas M.D. Anderson Cancer Center. In 1999 Berry and colleagues [56] evaluated the treatment of pregnancy-associated breast cancer with 5-Fluorouracil, Doxorubicin, and Cyclophosphamide (FAC: 500 mg/m^2 5-fluorouracil days 1 + 4; 50 mg/m^2 continuous 72-hour infusion of Doxorubicin days 1 through3; 500 mg/m^2 Cyclophosphamide day 1 of a 3-week cycle). This group reported no antepartum complications temporally attributed to systemic therapy and supported that Apgar scores, birth weights, and immediate postpartum health were normal for all children.

This data set expanded and was published recently by Hahn and colleagues [11] in September 2006. Fifty-seven women who had pregnancy-associated breast cancer were treated with FAC in the second and third trimesters, and parents/guardians were surveyed for longer-term follow-up (median follow-up duration 38.5 months). The authors reported no stillbirths, miscarriages, or perinatal deaths related to therapy. Only three patients delivered before 34 weeks gestational age, one being less than 29 weeks and associated with maternal preeclampsia. Only 6 children weighed less than 2500g. The most common documented neonatal complication was difficulty breathing, and 10% of neonates required mechanical ventilation. One child had a subarachnoid hemorrhage on postpartum day 2, coinciding with thrombocytopenia (platelet count 89 K/UL), and neutropenia. Finally, one child was born with Down syndrome. Only 2 of the 18 school-aged children required special attention at school, and the rest were thought to exhibit normal development [56].

There still remains a concern for anthracycline-associated fetal cardiotoxicity as children and adults reliably demonstrate a dose-dependent risk of cardiomyopathy with exposure. There have been several studies that support neonatal cardiac effects and in utero fetal death after exposure to idarubicin or epirubicin (among other agents) [62–64]. For this reason, Cardonick and colleagues endorse the use of doxorubicin rather than the aforementioned agents [60]. Meyer-Wittkopf and colleagues [65] performed fetal echocardiograms every 2 weeks in pregnant patients receiving doxorubicin and cyclophosphamide starting at 24 weeks. Using unexposed fetuses aged 20 to 40 weeks for comparison; the authors identified no notable difference in systolic function between the study and control groups. In fact, postnatal echocardiograms repeated until 2 years of age demonstrated no myocardial damage. Additionally, Peccatori and colleagues [66] support that epirubicin is preferable clinically in this setting given its better therapeutic index, fewer systemic and cardiac toxic effects, and shorter terminal half-life. These same authors relay their experience with epirubicin-based

regimens for pregnancy-associated breast cancer and report no severe maternal or fetal complications, only one case of vesicoureteral reflux, mirroring other authors' experiences [66–68].

Methotrexate is a known abortifacient, and it should be avoided during pregnancy [7,58]. There are several case reports that support the safety of taxanes in treating pregnancy-associated breast cancer, but nothing to support the safety of dose dense anthracycline therapy with or without taxanes during pregnancy [69–73]. Finally, there are only case reports documenting the use of trastuzumab on pregnancy. Watson describes a case of reversible anhydramnios, while two other case reports report no immediate fetal or neonatal complications [74–76]. Tamoxifen therapy during pregnancy has been associated with ambiguous genitalia and Goldenhar's syndrome while other authors note no fetal/neonatal complication [77–82]. Tamoxifen is not recommended during gestation [4].

Present recommendations for chemotherapy dosing in pregnancy are weight-based. This dosing, however, may be complicated by increased plasma volume, increased hepatorenal function, decreased albumin concentration, decreased gastric motility, and the theoretical possibility of amniotic sac third-spacing [7]. Also, chemotherapy should be avoided 3 to 4 weeks before delivery (following the mother's nadir) to reduce the risk of infectious complications and hemorrhage from pancytopenia [7,60].

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