

Pregnancy-Associated Breast Cancer

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ABSTRACT

The incidence of pregnancy associated with breast cancer can be expected to increase as maternal age at the time of pregnancy continues to increase. Women diagnosed with breast cancer during pregnancy have similar disease characteristics to age-matched controls. Surgical treatment may be performed as for the nonpregnant women. Radiotherapy and endocrine or antibody treatment should be postponed until after delivery. A multidisciplinary approach is recommended for optimal clinical decision-making. But physicians should be aggressive in the work-up of breast symptoms in the pregnant population to expedite diagnosis. It is generally agreed that therapeutic radiation, if necessary, should be delayed until completion of pregnancy.

Keywords: Pregnancy, Breast cancer, Breast lump.

INTRODUCTION

Breast cancer occurring during pregnancy or within the first year after delivery is considered to be pregnancy-associated breast cancer (PABC). It is the most common tumor in reproductive age. Around 3% of breast cancer occurs in pregnancy. This translates to a rate of 10 to 40 cases per 100,000 deliveries. Around 15% of breast cancers are seen in women of childbearing age, and there is evidence that the incidence of breast cancer in premenopausal women is increasing. As the average age of parity increases, the incidence of pregnancy associated breast cancer is also rising. When women delay their first pregnancy until the age of 35 years or more, the risk of breast cancer increases 3 times as compared to those who conceive prior to the age of 20.

I am pregnant is a phrase most women share with their partners and family with great joy, anticipation and exuberance. *I have breast cancer* is a phrase that all women dread. A small number of women experience both sets of emotions in quick succession after being diagnosed with breast cancer in early pregnancy. When both occur simultaneously, patients are terrified and distraught while their doctors are faced with the therapeutic dilemma involving surgical, obstetric, ethical, moral and psychological issues.

DIAGNOSIS

A high index of suspicion is required in the evaluation of a mass in the breast of a pregnant woman. During pregnancy, a woman's body undergoes substantial physiological changes, including enlargement of the breasts, which makes it more difficult to notice the small lumps that forewarn of cancer. To detect breast cancer, pregnant and lactating women should practice self-examination and be examined by a physician as a part of routine prenatal care. An enlarging mass that persists without regression and other primary or secondary signs of

malignancy, such as nipple retraction, fixation of a mass to skin, skin thickening, dimpling or development of axillary adenopathy should be considered as indications of possible malignancy, and a diagnostic work-up should be initiated.

It has been reported that the average delay from initial symptoms to treatment exceeds 5 months.¹ The increased vascularity and lymphatic drainage from the gravid or lactating breast are other factors that aid metastatic spread. Because of this delay, cancers are typically detected at a later stage than in a nonpregnant age matched group. Masses discovered during routine examination or detected by the patient require evaluation. Significant physician delay has been noted in virtually all series of PABC. Also, it has been reported that a pregnant woman has 2.5 fold higher risk of being diagnosed with metastatic breast cancer and a decreased chance of diagnosis of stage I.² Similar findings have also been reported by other authors.^{3,4}

Mammography is not performed routinely due to concern about fetal irradiation. However, a bilateral mammographic examination of breasts with modern equipment would yield less than 50 mrad (500 µGy) to the human embryo,⁵ which is well below 10 rad (100 mGy) toxic level. However, it is likely that the sensitivity of mammography is diminished during pregnancy as well as lactation due to increased glandularity and water content of the breast.^{6,7} If a worrisome breast lump or abnormality is found after birth when a woman is breastfeeding, diagnostic mammography and/or other breast imaging exams should not be delayed. Mammography is considered safe and can be accurate for women who are breastfeeding when performed with care. Some suggest that the breast should be completely emptied of milk immediately before the mammogram, either via nursing or breast pump. This decreases the density through which the X-rays must penetrate and helps to improve image quality.

Breast ultrasonography is a good, inexpensive first imaging choice for the pregnant woman, and can distinguish between cystic and solid lesions⁶ in 97% of patients. It may confirm the presence of a mass when physical examination is equivocal and the woman complains of pain or tenderness. The decision to observe the mass in the pregnant woman is fraught with hazards as physical examination becomes progressively more difficult with increasing breast enlargement and vascularity as pregnancy progresses.

Magnetic resonance imaging itself is associated with two kinds of risks to the fetus: Heating and cavitation. For the diagnosis of metastases, MRI is preferred to ultrasonography for hepatic imaging. It is also the safest and most sensitive way to scan the brain and for bony metastases.

Fine needle aspiration (FNA) of a suspected lesion in the breast carries the risk of both falsely positive and negative results. The hyperproliferative cellular state of the mammary tissue leads to the possibility of false positive diagnosis of malignancy. On the other hand, the needle technique runs the risk of missing the mass.⁷ The nursing mother should be advised to stop breastfeeding and to allow milk production to cease prior to biopsy. The cessation of lactation will decrease the risk of milk fistula and vascularity of the breast. Although, inflammatory breast carcinoma is not more common in PABC than in the general population with breast cancer, an incidence ranging from 1.4 to 4% is reported.⁸ For this reason, all abscesses that are surgically drained should have a biopsy of the wall and any suspicious area.

Excisional biopsy is a useful adjunct for the confirmation. However, an increased vascularity of the breast carries a little risk of postoperative hematoma, infection and milk fistula. There is no evidence to suggest that a breast biopsy constitutes a risk to the mother or the fetus.

Determination of receptor hormonal status by immunochemistry technique, if available should be availed. This helps in determining the indication for hormonal therapy and chemotherapy.

Differential Diagnosis of Breast Carcinoma in Pregnancy

1. Benign lesions/lumps unique to pregnancy and lactation. These may include fibroadenomas, sarcomas, fat necrosis, cysts due to fibrocystic disease, galactoceles, leiomyomas, sebaceous cysts, histiocytomas, adenolipomas, neurofibromas, granular cell tumors, sarcoidosis, tuberculosis, etc. The lactating adenoma is a lesion, unique to pregnancy and lactation, characterized histologically by florid lactational changes and a tubuloalveolar appearance of the glands. Infarction may occur in an existing fibroadenoma or lactating adenoma. Galactoceles are milk-filled single or multiple nodules caused by obstruction of the ductal system. They mostly occur due to cessation of lactation, may occur after many months, and usually yield milk on

pressing. Aspiration may be both diagnostic and curative or excision may be done if it recurs.

2. Bloody nipple discharge during pregnancy and lactation. This finding per se may not signify a grave consequence. Although it is a sign of malignancy, it is usually associated with a palpable mass. Pregnancy induces changes in the ducts, which lead to the formation of delicate intraductal epithelial spurs that are easily traumatized and shed, thus resulting in a bloody discharge. Although cytologic study of the bloody discharge is indicated, it may be difficult to interpret because the proliferative changes associated with pregnancy may confound the diagnosis of a malignant process.

If a bloody discharge is not accompanied by a palpable mass and if the cytology is not suggestive of malignancy, it is appropriate to observe the patient clinically for several months postpartum. If the bloody discharge persists for more than 2 months after delivery, is localized to one duct, or is associated with a palpable mass, mammography and biopsy may be indicated. The presence of blood is not a contraindication to breastfeeding. Bloody discharges may commonly be associated with the initiation of breastfeeding and usually cease after breastfeeding.

Pathology and Biology

The pathology is similar in age matched pregnant and non-pregnant women, including the incidence of inflammatory carcinoma of 1.5 to 4%.⁹ However, recent histopathological reports of 14 cases found that breast carcinomas diagnosed in pregnancy are mostly estrogen and progesterone receptor negative with a higher incidence of grade III invasive ductal carcinomas.¹⁰ The stage distribution at the time of presentation is as follows: stage I: 28%, stage II: 30% and stage III and IV: 42%.¹¹ Very little information is available about the accuracy and the value of steroid hormone receptor status during pregnancy. Most probably, pregnant women like most young patients, are estrogen (ER) receptor and progesterone receptor (PR) negative. No data on pregnant patients with accurate hormone receptor status exist for formulating recommendations on therapeutic abortions, hormonal manipulation or subsequent pregnancies.

Treatment of Pregnancy-associated Breast Cancer

The treatment options depend on the stage of the disease and the age of the fetus. It is very difficult to make general comments about treating such patients. The potential risks and benefits have to be evaluated for each patient differently.

Surgery

About 60% of pregnant women with breast cancer present with early stage cancer, stages I and II breast cancers are best treated

with surgery. A modified radical mastectomy is currently the standard treatment for early stage disease.⁸ Risks of surgery during pregnancy include spontaneous abortion and preterm labor. It can usually be performed safely during pregnancy with minimal risk to the fetus and mother, particularly in the second and third trimesters. When compared with radiation therapy and chemotherapy, surgery is least likely to affect the pregnancy. This operation entails the preservation of the pectoralis major and minor muscles, providing better arm motion, thoracic outline and reducing the incidence of postoperative lymphedema of the arm.

Because breast-conserving surgery (lumpectomy or quadrantectomy) generally employs postoperative radiotherapy, this modality is discouraged. Although this surgery can be performed during pregnancy, the radiation therapy required to complete local therapy for the breast must be delayed until after delivery. This is most suitable when PABC is diagnosed during the late third trimester.

Radiotherapy

Radiation therapy generally is not offered because it poses two kinds of risks: Teratogenicity and induction of childhood malignancies and hematological disorders. An external irradiation dose of 5000 cGy to the breast exposes the fetus to at least 10 to 15 cGy. The part of the fetus located immediately below the diaphragm, late in pregnancy, is exposed to several hundred centigrays.⁶ Because much of this dose comes from internal scatter of radiation within the body of the mother, abdominal shielding is only partially effective. A general guideline is to limit the total fetal dose to 5 cGy.¹² Radiation therapy is rarely used if other alternatives exist.

Chemotherapy

All chemotherapeutic agents are theoretically teratogenic and mutagenic. The risk of malformations when chemotherapy is administered in the first trimester has been estimated to be approximately 10% for single agent chemotherapy regimens and 25% for combination chemotherapy.¹³ Their use may result in fetal growth restriction, fetal malformation, spontaneous abortion, or fetal death. It is important to differentiate teratogenic and mutagenic effects from those related to suboptimal uterine environment or to maternal toxicity, such as neutropenia, infection, thrombocytopenia, or myocardial toxicity. Chemotherapy should be given only after 14 to 15 weeks of gestational age. The first trimester is the most critical time period with respect to exposure to chemotherapy. The blastocyst is resistant to teratogens in the first 2 weeks of life. If it is not destroyed, a surviving blastocyst exposed during the first 2 weeks will not manifest any abnormalities from a chemotherapeutic agent. The 3rd to 8th week of development, 5 to 10 weeks of gestational age, is the period of maximal susceptibility to teratogenic agents. With the exception of brain and gonadal tissue, organogenesis is complete by 13 weeks of gestation.

If chemotherapy induces severe damage early in gestation, spontaneous abortion results. If, however, sublethal damage occurs between second and tenth week of gestation, teratogenesis may occur. After organogenesis is complete, the risk for birth defects induced by chemotherapy is decreased and intrauterine growth restriction becomes the dominant effect. Approximately, 10 to 20% of infants exposed to cytotoxic agents during the first trimester have major malformations as compared with a rate of 3% in the general population. In general, chemotherapy should be delayed whenever possible until after the first trimester. Up to 80% patients of PABC are ER- and PR-negative. During the first trimester cyclophosphamide, methotrexate and 5-fluorouracil (CMF) should not be used due to toxicity of folate antagonists. If chemotherapy has to be given during first 3 months, we should use a combination of cyclophosphamide, doxorubicin (adriamycin), 5-fluorouracil (CAF). CMF can be used safely during the second and third trimesters. Chemotherapy is contraindicated in lactating women as many chemotherapeutic agents including cyclophosphamide, doxorubicin, methotrexate, hydroxyurea and cisplatin are secreted in breast milk. Otherwise, breastfeeding should be stopped before initiating the chemotherapy. Still all other modalities of treatment are available during lactation. If surgery is planned, breastfeeding should be stopped to reduce size and vascularity. Stopping lactation does not improve survival of the mother.

Hormonal Therapy

Tamoxifen citrate, a selective ER modulator frequently used in breast cancer regimens, is associated with fetal anomalies like oculoauriculovertebral dysplasia (Goldenhar syndrome) and ambiguous genitalia. The long-term effects of tamoxifen use, and whether it may increase gynecological cancers in daughters (as diethylstilbestrol does) are unknown; in pregnant rats, tamoxifen has been associated with breast cancer in the female offspring.¹⁴ Oophorectomy is not recommended in conjunction with pregnancy-associated breast cancer, in part because patients are likely to have ER-negative tumors that are not affected by endogenous hormones.

General Plan for Treatment of Breast Cancer with Pregnancy

Factors affecting the Treatment Plan of Breast Cancer with Pregnancy

The treatment is individualized according to individual case circumstances that include:

1. Gestational age in which the cancer was discovered
2. Surgical staging
3. Pathology of the tumor
4. Hormonal receptors status
5. Involvement of lymph nodes
6. Number of children the lady has.

Stage I and II are operable and are treated by modified radical mastectomy with or without postoperative irradiation, hormone therapy or chemotherapy. Stage III and IV are inoperable and are treated by simple mastectomy as palliative measure for pain and fungation followed by palliative chemotherapy, hormone therapy or irradiation.

First and second trimester: Termination of pregnancy could be the choice to allow freehand dealing with the cancer, especially in late stages and positive lymph nodes sampling. Those cases will need postoperative radiation and/or chemotherapy. Both of them are contraindicated in that period of pregnancy.

Third trimester: Surgical treatment should be applied without delay; pregnancy should be terminated once the fetal maturity allows that. Postpartum radiotherapy and chemotherapy can be given with prevention of lactation in case of chemotherapy.

Metastasis of Breast Cancer to Fetus

Metastatic spread to the placenta has been reported but is extremely rare.¹⁵ Placental metastasis has generally been reported in association with widespread metastatic disease. Spread to the fetus has never been reported, although such spread has been reported for melanoma, hematopoietic malignancies, hepatoma, and choriocarcinoma. Careful histologic examination of the placenta is required even if the placenta is grossly normal. The fear that breast cancer may spread to the fetus is a major concern of patients.

Prognosis

Most series report that actual survival and disease-free survival are the same in gestational and nongestational women with breast cancer matched by age and stage. However, pregnant women have a significantly higher risk of being diagnosed with metastatic disease. The detection of breast cancer in advanced stages during pregnancy is probably related to delayed diagnosis and compromises survival. Young women, pregnant or not, usually have ER-negative tumors, which have a biologically aggressive course and carry a poor prognosis. Thus, physiological elevation of circulating hormones in pregnancy should not affect the aggressiveness of ER-negative tumors. This is supported by the similar survival of matched nonpregnant controls and by the lack of survival benefit with termination of pregnancy. Studies have also revealed that prior and subsequent pregnancy are important prognostic factors.

Should Termination of Pregnancy be Considered in PABC?

Most recent reports do not show an advantage in survival after therapeutic abortion. Hormonal factors appear to play an important role early in development of breast cancer; however, pregnancy itself does not appear to influence the outcome of an established breast cancer. The finding of a high percentage of ER- and PR-negative tumors in most series of PABC give little

theoretical grounds for pregnancy termination. Most series of PABC reporting on receptor status indicate that as many as 80% of lesions are ER- and PR-negative.³ Study of histopathological parameters and immunoreactivity for estrogen and progesterone receptors, c-erbB2 and c-erbB4 showed low frequency of hormone receptors, BRCA1, p27, cyclin E, D1 and high expression of c-erbB2. These findings gave the impression that PABC was an aggressive tumor.

The sole advantage of pregnancy termination is that full and complete treatment of aggressive or advanced disease with chemotherapy, radiotherapy and surgery may be instituted without consideration of the effects on the fetus. The medical recommendation to terminate a pregnancy should be based on whether pregnancy will present a significant obstacle to effective therapy and whether the fetus will sustain harm as a result of therapy. Because pregnancy has no effect upon the course of disease, the termination of pregnancy does not ameliorate disease. Spontaneous abortions and prematurity are not increased in pregnant women with malignancy. As chemotherapy cannot be given before 14 to 15 weeks of pregnancy, therapeutic abortions may be considered in the first or second trimester, so that metastatic disease can be treated promptly, particularly if the patient is ER-positive.

Consequences of Pregnancy in Patients with a History of Breast Cancer

As more young people are surviving cancer, more women are considering whether they should have a baby after having cancer. In general, pregnancy after cancer is considered safe for both the mother and the baby, and pregnancy does not appear to increase the chances of cancer recurring. Chemotherapeutic agents significantly affect the subsequent fertility. The risk of premature ovarian failure induced by chemotherapy can be estimated from the women's age, the agent used and the total dose. Alkylating agents, such as cyclophosphamide cause amenorrhea through direct ovarian depression. Although cyclophosphamide is a major cause of ovarian failure, methotrexate and 5-fluorouracil are not. Approximately, 50% of women less than 35 years of age resume menses after a full course of adjuvant chemotherapy. As a general rule, cancer identified prior to conception should be adequately treated with appropriate follow-up before pregnancy is attempted. Once successfully treated, few malignant diseases absolutely preclude future pregnancy. Several studies have suggested that women who become pregnant after treatment for breast cancer demonstrate a trend towards improved prognosis when compared with women not subsequently pregnant.⁴ Abortion does not improve survival, and termination of pregnancy is considered only in women with recurrent disease.

Pregnancy does not appear to compromise the survival of women with a previous history of breast cancer based on a limited retrospective data, and no deleterious side effects have been demonstrated in the fetus. Some physicians recommend that patients wait for 2 years after diagnosis before attempting

to conceive. This allows early recurrence to become manifest, which may influence the decision to become a parent.

Does Pregnancy Protect from Breast Cancer?

Every woman's hormone levels change throughout her life for a variety of reasons, and hormone changes can lead to changes in the breasts. Hormone changes that occur during pregnancy may influence a woman's chances of developing breast cancer later in life.

Pregnancy-related Factors that Protect Against Breast Cancer

1. The younger woman has her first child, the lower risk of her developing breast cancer during her lifetime.
2. A woman who has her first child after the age of 35 has approximately twice the risk of developing breast cancer as compared to a woman who has a child before age 20.
3. A woman who has her first child around age 30 has approximately the same lifetime risk of developing breast cancer as a woman who has never given birth.
4. Having more than one child decreases a woman's chances of developing breast cancer. In particular, having more than one child at a younger age decreases a woman's chances of developing breast cancer during her lifetime.
5. Although not fully understood, research suggests that pre-eclampsia is associated with decrease in breast cancer risk in the offspring, and there is some evidence of a protective effect for the mother.

After pregnancy, breastfeeding for a long period of time (e.g. a year or longer) further reduces breast cancer risk by a small amount. Researchers have found that a substance discovered in breast milk can kill cancer cells called HAMLET (human alpha-lactalbumin made lethal to tumor cells). The substance is a combination of a protein and a fatty acid and was discovered by chance a few years ago when researchers were studying the antibacterial properties of breast milk. Previous laboratory experiments have shown that HAMLET kills 40 different types of cancer.

Pregnancy-related Factors that Increase Breast Cancer Risk

1. After a woman gives birth, her risk of breast cancer is temporarily increased. This temporary increase lasts only for a few years.

2. A woman, during pregnancy, who took DES (diethylstilbesterol), a synthetic form of estrogen that was used between the early 1940s and 1971, has a slightly higher risk of developing breast cancer (so far, research does not show an increased breast cancer risk for their female offspring who were exposed to DES before birth. Those women are sometimes referred to as *DES daughters*).

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