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# Pregnancy-associated Breast Cancer

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**Abstract:** As women delay childbirth, the incidence of pregnancy-associated breast cancer is expected to increase. A high degree of suspicion is necessary to ensure timely investigation and diagnosis of breast cancer in a pregnant woman with a suspicious breast lump. Surgery as an initial approach is more suitable when diagnosis is made in the first trimester and systemic therapy can be delayed to second trimester. Diagnosis of breast cancer in the later stages of pregnancy can be managed with primary chemotherapy or surgery. A multidisciplinary approach involving medical and surgical oncologists, high-risk obstetric care, genetic counselors, pharmacists, radiation oncologists, and neonatologist is highly recommended for the successful management of cancer and pregnancy.

**Key words:** breast cancer, pregnancy, epidemiology

## Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring anytime during gestation, lactation, or within 1 year after delivery. The management of PABC is challenging in many

respects; the breast undergoes multiple physiological changes during pregnancy making the diagnosis and the follow-up of a lump clinically difficult, the diagnostic and staging work up should not affect the development of the fetus or the offspring and yet be effective, and finally, the management should take into account the effects of therapy and timing of delivery on development of the fetus or offspring while ensuring the optimal growth and pulmonary maturity of the fetus. Thus, the diagnosis of cancer during pregnancy adds complexity to both the management of the pregnancy and cancer. However, current available data demonstrate that the pregnant cancer patient can receive optimal treatment with a multidisciplinary approach incorporating a medical oncologist, surgical oncologist, radiation oncologist, radiologist, and maternal fetal medicine specialist. Early termination of pregnancy does not improve the outcome of PABC. Hence, an informed decision with the best interest of the mother and developing fetus in mind has to be made in a multidisciplinary manner with active involvement of the patient all along the process. The goals of therapy are to maximize the potential for cure for the cancer

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while minimizing the risk to the fetus from cancer treatment.

## ***Epidemiology***

Breast cancer is the second most common malignancy diagnosed in pregnancy (after cervical cancer). The incidence is between 1 in 3000 and 1 in 10,000 pregnancies and comprises about 0.2% to 3.8% of all breast cancers diagnosed in women under the age of 50 years. Alternatively, 10% to 20% of breast cancers diagnosed in women 30 years or younger are associated with pregnancy or postpartum. The Surveillance Epidemiology and End Results program estimates the rate of breast cancer diagnosed in women less than 44 years at 215.8 per 100,000. As women tend to delay childbearing into their third and fourth decades, the incidence of PABC is expected to increase.

## ***Clinical Presentation and Diagnosis***

The clinical presentation of breast cancer as a painless lump in the breast is similar in both pregnant and nonpregnant women. Occasionally, the refusal by an infant to nurse from a lactating breast may be a sign of an underlying occult carcinoma and is described as the milk rejection sign.

The challenge in diagnosing PABC is related to the fact that the breast undergoes several physiological changes including increased glandular changes, size, and density during gestation and lactation. Any lump that is persistent in a pregnant patient beyond 2 to 4 weeks needs further work up. A high degree of suspicion is required to diagnose these cancers without significant delay. Most recent studies indicate that most PABCs are diagnosed after a delay of 1 to 2 months.<sup>1</sup> In a mathematical model assessing tumor progression over time, a 1-month delay in the

treatment of primary tumor increased the risk of axillary metastases by 0.9% to 1.8%.<sup>2</sup> This perhaps contributes to the higher percentage of pregnant women being diagnosed with larger tumors and node-positive breast cancer. A list of differential diagnosis for breast lumps in pregnancy is outlined in Table 1.

Breast ultrasonography is the ideal first step toward investigating a suspicious breast lump in a pregnant woman. An ultrasound can distinguish between a solid and cystic lesion without the risk of radiation exposure to the fetus. In addition, the axillary basin can be evaluated for any suspicious lymph nodes. If palpable or suspicious lymph nodes are present, these can be biopsied by fine needle aspiration (FNA) biopsy under ultrasound guidance.

Mammography is associated with a high false-negative rate during pregnancy, with sensitivity rates ranging from 63% to 78%, with the higher percentages reported in some of the most recent studies.<sup>3,4</sup> The changes in the breast that result in the high false-negative rate are the increased water content and change in the distribution of fat. Mammography with abdominal shielding is considered safe during pregnancy as the average glandular dose of 0.02 to 0.04 Gy results in a very negligible radiation dose of only 0.00004 Gy to the fetus. Hence, mammography is still a useful and safe tool during pregnancy and bilateral mammogram is often performed if ultrasound is suggestive of malignancy.

No published data currently exists regarding the use of breast magnetic resonance imaging (MRI) during pregnancy. Although gadolinium-enhanced MRI is more sensitive than mammography for detecting invasive breast cancer, several disadvantages limit its use in pregnant women. Gadolinium crosses the placenta and is associated with fetal abnormalities in rats. Hence MRI is not recommended for diagnosis of breast cancer during

**TABLE 1. Differential Diagnosis of a Breast Mass in a Pregnant or Lactating Woman**

Invasive breast cancer
Lactating adenoma
Fibroadenoma
Fibrocystic disease
Milk retention cyst
Abscess
Lipoma
Hamartoma
Lobular hyperplasia
Phyllodes tumors
Sarcoma

pregnancy; MRI with gadolinium may be performed during the postpartum period if necessary.

Definitive diagnosis of any breast lump is achieved by tissue biopsy and should be performed for any clinically suspicious lump. This can be safely performed by core needle biopsy, under local anesthesia. Alternatively, FNA can be performed; however, it may pose a diagnostic challenge for the pathologist secondary to the pregnancy-associated changes in the breast architecture. The pathologist should be made aware that the specimen is from a pregnant woman. Complications resulting from a biopsy for a suspected PABC include formation of a milk fistula in a lactating women and a slight increased risk of bleeding. Stopping breast feeding or medical suppression of lactation will reduce the risk of development of milk fistula. Excisional biopsy can be performed for benign breast lumps. Immunohistochemical stains for the estrogen receptors (ER), progesterone receptors (PR), and Her2 should be performed on biopsied tissue from PABCs.

### **Staging**

The tumor, node, and metastasis staging system of the American Joint Committee on Cancer is appropriate for pregnant women with breast cancer. Women with PABC often present with a more

advanced stage because of the diagnostic challenges that lead to delayed diagnosis. It is essential to begin with a thorough history to evaluate for any possible symptoms attributable to underlying malignancy or metastasis. A complete physical examination should be performed to clinically assess for the extent of the primary disease and for possible metastasis, in particular axillary nodal metastasis.

Women with PABC who are asymptomatic and clinically node negative do not require further staging work up for detection of distant metastasis. In women with symptoms and with larger tumors (such as T3 and T4 lesions and clinically palpable nodes), a complete radiologic staging evaluation is warranted. Clinically palpable lymph nodes should be assessed further by ultrasound-guided FNA. In women with nonpalpable axillary nodes, sentinel lymph node biopsy may be performed and is discussed in the section below.

Breast cancer most commonly metastasizes to the distant organs such as bone, liver, lung, and lymph nodes. Thus, independent of pregnancy, axial imaging such as computed tomography (CT) is often used for radiographic staging of the disease. CT scans are generally avoided in pregnancy because of the large cumulative radiation dose because of repeated imaging. Chest radiograph can be safely performed in pregnancy with abdominal shielding. If further evaluation of the chest is required, MRI without gadolinium can be performed as the safety of gadolinium (category B) in pregnancy is yet not established. Although less sensitive than CT scans, abdominal ultrasound is a safe method to evaluate for liver metastases in pregnancy. MRI without contrast of the liver can be performed if further assessment is required.

To assess the skeleton for metastasis during pregnancy, low-dose bone scan or thoracic and lumbar spine MRI without contrast is recommended. Low-dose bone

scans expose the fetus to 0.08 rad (as compared with 0.19 rad with a conventional bone scan).<sup>5</sup> When bone scans are performed, good maternal hydration and frequent voiding is recommended to minimize the fetal exposure to radionuclide. Plain x-rays of the symptomatic bony sites can also be used to assess for metastatic disease. Any suspicious lesion on the above imaging which needs further work up should be considered for a biopsy. MRI of the brain, if indicated is performed without contrast.

### **Pathology**

Majority of breast cancers in pregnancy are infiltrating ductal carcinomas that are poorly differentiated. Most studies have reported a lower percentage of PABCs expressing ER or PR (approximately 25%) than the 55% to 60% reported in nonpregnant premenopausal women. Many of the older studies reporting the incidence of ER/PR-positive tumors in PABC used the ligand-binding assay but some of the more recent studies using immunohistochemical staining for ER/PR still report a lower incidence of ER/PR positivity in PABCs. The high circulating levels of estrogen and progesterone during pregnancy down-regulate the ER levels and contribute to this low ER-positive status is a potential explanation for this finding.

Her2 is a tyrosine kinase belonging to the epidermal growth factor receptor family and approximately 20% to 25% of breast tumors have amplification of this gene resulting in over expression of the protein (which is detected by immunohistochemistry). Her2 over-expressing tumors are typically more aggressive and associated with a poor prognosis. The prevalence of Her2 over expression in PABC is slightly higher than that seen independent of pregnancy, with rates reported between 28% and 58%.

In addition, among women with PABC, there is a higher incidence of aggressive inflammatory breast cancers, which are 2.5 times more likely to have distant metastatic disease at diagnosis.

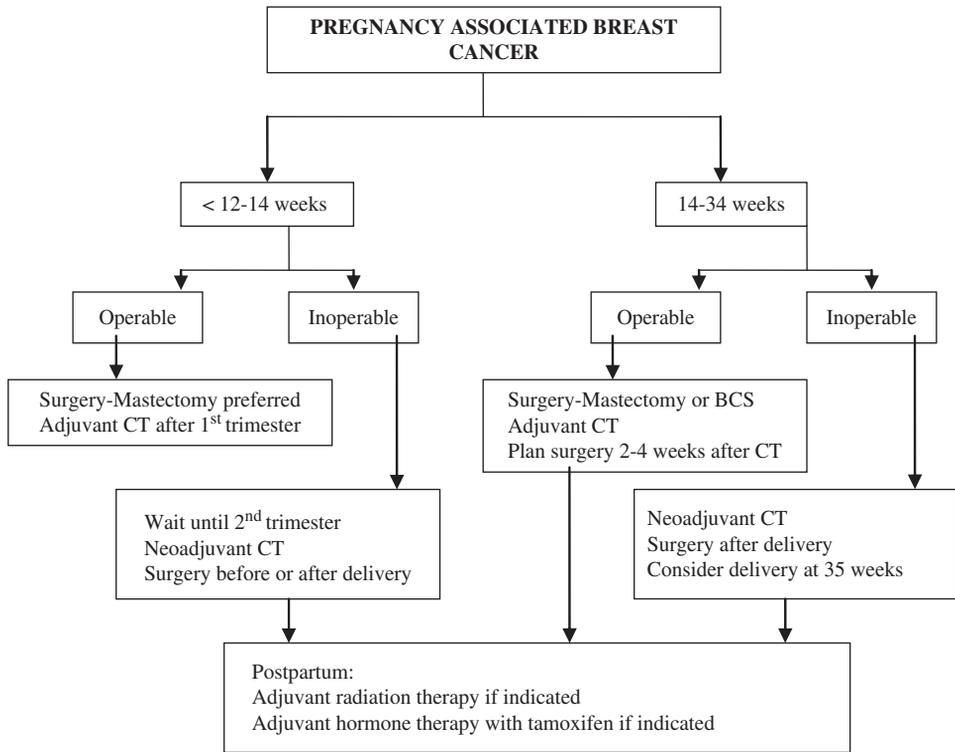
### **Treatment**

Breast cancer occurring in the postpartum period is treated in the same way as breast cancer occurring in the nonpregnant woman. Breast feeding is contraindicated in patients receiving systemic therapy. Treatment of breast cancer during pregnancy follows the same principles as the management of breast cancer in nonpregnant patients with some key exceptions. The goal of treatment is directed at providing the best curative treatment for the cancer with minimal or no harm to the fetus and to maximize the gestational period and ensure safe delivery of the fetus. Although medical termination of pregnancy should be discussed if a diagnosis of PABC is made early in the pregnancy, this has not been shown to improve the overall outcome of the cancer. A treatment algorithm is outlined in Figure 1.

#### **EARLY BREAST CANCER**

##### ***Loco-regional Therapy***

Surgery is the definitive treatment for localized breast cancer. Surgery and the use of general anesthesia are currently considered to be safe during any trimester of the pregnancy. Mastectomy and breast-conserving therapy followed by radiation are the 2 options for definitive surgery. Mastectomy eliminates the need for breast irradiation and hence eliminates the fetal risks associated with radiation. However, if cancer is diagnosed late in the second or third trimester, lumpectomy can be performed with plan for radiation after delivery. Breast reconstruction, if



**FIGURE 1.** Treatment algorithm for management of pregnancy-associated breast cancer. BCS indicates breast-conserving surgery; CT, chemotherapy.

desired is usually delayed until after delivery.

Axillary staging is a very important aspect of therapy as the nodal status affects locoregional therapy and choice of adjuvant therapy. The standard of care for axillary staging in clinically node negative, nonpregnant women is sentinel lymph node biopsy. Although some recent studies illustrate the potential safety of this approach in pregnant women, several concerns still exist. Supravital dyes such as isosulfan blue dye should not be used in pregnancy because of potential anaphylactic reactions resulting in fetal loss. Small studies demonstrate that with the use of double filtered technetium sulfur colloid, sentinel lymph node biopsy can be safely performed in pregnant women.<sup>6</sup> However, until further data are available, sentinel lymph node biopsy

should only be recommended to pregnant women in the context of a clinical trial.

In summary, mastectomy with axillary lymph node dissection remains the standard of care for women with early stage, operable breast cancer diagnosed in the first and early second trimester. Breast conservation surgery with lumpectomy and axillary lymph node dissection is an option for women diagnosed in the late second or third trimester when radiation therapy can be pursued after delivery. Decisions regarding timing and type of surgery should take into consideration the need for adjuvant chemotherapy and radiation therapy and avoiding delays beyond 6 months from the time of definitive surgery in initiating adjuvant radiation.

Adjuvant radiation therapy improves local control and survival in breast cancer. However, the increased risk to the fetus in

the form of teratogenicity, induction of childhood malignancies, and hematological disorders preclude the use of radiation therapy in the management of breast cancer during pregnancy. The excess cancer risk to a fetus receiving radiation is 6.57 cases per 10,000 children per rad per year. Typical external beam radiation dose to the breast range from 45 to 60 Gy, which could result in a fetal radiation exposure of 3.9 to 15 rad in the first trimester to as much as 200 rad in late third trimester.<sup>7</sup> Despite several anecdotal reports of normal infants born to mothers exposed to radiation, radiation therapy is not recommended during pregnancy as absence of risk to the fetus cannot be guaranteed.

### **Systemic Therapy**

Women with PABC are often candidates for systemic chemotherapy as they tend to present with higher stage disease and have tumors that are more commonly ER negative, consistent with guidelines used to treat similar stage cancers diagnosed independent of pregnancy. In patients with locally advanced (T3 or clinically node-positive) breast cancer, systemic chemotherapy may be given before definitive surgery (neoadjuvant chemotherapy) for downstaging of the tumors and to obtain better surgical outcomes. Neoadjuvant chemotherapy can also be administered in pregnant women who want to avoid mastectomy. This approach provides systemic therapy first and the surgery can be delayed close to or after delivery and radiation therapy can be done subsequently after delivery.

In general, adjuvant chemotherapy is considered for all premenopausal women with node-positive breast cancer or tumors that are poorly differentiated, ER negative and > 1 cm, and Her2-positive tumors. There are no randomized controlled trials evaluating the safety of the various chemotherapy regimens in breast cancer. Most of the data are obtained from the use of the drugs or similar

drugs in breast cancer or other cancers occurring in pregnancy. Information regarding the effects of chemotherapy administered during pregnancy is largely compiled from case reports and small case series. Dosing of chemotherapy during pregnancy is also complicated by the physiological changes in plasma volume, increased hepatic and renal clearance, third spacing of drugs in the amniotic sac fluid, changes in serum albumin, and decreased gastric emptying. Nonetheless, the dosing of chemotherapy is the same as in non-pregnant females.

Organogenesis occurs from 10 days to 12 weeks after implantation and carries the greatest risk for spontaneous abortion and fetal death secondary to chromosome or congenital abnormalities. In general, chemotherapy is best avoided during this period of critical organogenesis if the delay in chemotherapy would not compromise the health of the mother. If a diagnosis of PABC is made very early in pregnancy, medical termination of pregnancy can be discussed with the patient. There are no studies of chemotherapy in the first trimester other than anecdotal reports of patients becoming pregnant while on chemotherapy.

Chemotherapy is generally considered to be less risky in the second and third trimester. One review reported a 1.3% risk of fetal malformation in 150 women given chemotherapy in second or third trimester compared with risk of 16% in the first trimester chemotherapy.<sup>8</sup> Approximately 50% of infants exposed to chemotherapy in the second and third trimester manifest intrauterine growth retardation, prematurity, and low birth weight.

Anthracyclines and taxanes are considered standard of care in the management of node-positive breast cancer in nonpregnant women. Anthracycline (doxorubicin and cyclophosphamide)-based therapy with or without fluorouracil/adriamycin/cyclophosphamide (FAC) are the most

common regimens used in women with PABC. In the largest prospective study of 57 pregnant women treated with FAC regimen administered either as adjuvant (n = 32) or neoadjuvant (n = 25) therapy in the second or third trimester, there were no reported stillbirths, miscarriages, or perinatal deaths. The median number of FAC cycles given in this study was 4 (range, 1 to 6). The mean gestational age at delivery was 37 weeks. Patients on this study were then followed by mail or telephone to determine the long-term outcome of the children exposed to chemotherapy in utero. Three children had congenital abnormalities: one each with Down syndrome, ureteral reflux, and club foot. The other children were found to have normal developmental milestones during the follow-up ranging from 2 to 157 months.<sup>9</sup> Of the 25 patients who received neoadjuvant chemotherapy with FAC, 6 had a complete pathologic response, whereas 4 had no tumor response to chemotherapy and eventually died from their disease. PABC is reported to be as chemosensitive as non-PABC in the neoadjuvant setting.<sup>10</sup>

Another group reported results from a study of 20 patients with PABC with single agent epirubicin (E) administered weekly.<sup>11</sup> Weekly E was well tolerated and no congenital anomalies other than 1 child with polycystic kidney disease. However, single agent E is not considered a standard treatment option for adjuvant therapy. Other smaller case series have been reported with use of abdominal circumference, FEC, and epirubicin/cyclophosphamide in pregnancy. Methotrexate should be avoided in all stages of pregnancy because of the possibility of third spacing in the amniotic fluid as well as its abortifacient and teratogenic effects in early pregnancy. Currently, there are no reports of use of dose dense regimens for PABC.

There is not an extensive experience with taxanes in the gestational patient. In breast cancer patients, often the taxane

therapy is done after delivery. In a recent review of 40 pregnant women who received taxanes, there was no report of intrauterine deaths or congenital malformations other than 1 infant with pyloric stenosis.<sup>12</sup> Another concern regarding the taxanes is the potential for lowered serum concentrations in pregnancy because of the activation of the P-450 system in pregnancy resulting in increased drug metabolism.<sup>13</sup>

Chemotherapy in general should be avoided for 3 to 4 weeks before anticipated time of delivery to reduce myelosuppression and potential for peripartum complications.

### *Trastuzumab*

Incorporation of trastuzumab therapy for HER-2/neu-positive disease is the standard of care in the adjuvant and metastatic setting. There have been 13 case reports of the use of trastuzumab in pregnancy. Of the 13 patients, 1 patient elected to have abortion and was found to have an ectopic pregnancy. Eight of the other 12 patients developed oligohydramnios. Four neonatal deaths were reported after exposure to trastuzumab secondary to respiratory and renal failure. The increased risk of oligohydramnios is thought to be due to trastuzumab down-regulating the strong expression of Her2 on the renal epithelium. Surprisingly, there have been no reports of serious fetal cardiac effects. There is a case report of significant deterioration in maternal cardiac function when trastuzumab was administered during pregnancy. Currently, trastuzumab has a black box warning for use in pregnancy and treatment with trastuzumab should be delayed after delivery.

### *Tamoxifen*

For women who have hormone receptor-positive disease, therapy with tamoxifen is best deferred until after delivery. Pre-clinical models have shown that in utero exposure to tamoxifen increased the incidence of genital abnormalities.

Treatment with tamoxifen has been associated with vaginal bleeding, spontaneous abortion, birth defects, and fetal death. In addition, the long-term effects of tamoxifen on the female offspring are unknown.

### **METASTATIC BREAST CANCER**

Reports of metastatic PABC are generally single case reports describing patients who were incidentally found to be pregnant while being treated for their metastatic disease. Evidence-based recommendations for the management of metastatic breast cancer in pregnant women are very limited compared with those in early breast cancer. Anthracycline-based regimens are considered safe in second and third trimester and there have been 3 case reports of docetaxel being used without much consequence. However, patients may not have a prolonged response to a single agent (lasting 2 trimesters) and may need to switch to other agents. Delaying therapy for long periods of time may adversely affect the welfare of the mother. Hence, it is reasonable to discuss medical termination of pregnancy in a patient with metastatic breast cancer. Bisphosphonates are commonly used to reduce skeletal-related events in breast cancer patients with bone metastases. Reports of use of bisphosphonates in 51 pregnant patients for different indications did not reveal any increase in maternal or fetal morbidity.<sup>14</sup> A more recent report in 21 patients treated for osteoporosis did not reveal any increase in adverse effects on the fetus or the pregnancy.<sup>15</sup> Zoledronic acid and pamidronate, the 2 most commonly used bisphosphonates in metastatic breast cancer are categorized as pregnancy category D and the risks must be weighed against the potential benefits in an individual situation.

### ***Supportive Care***

Use of antiemetics such as the 5HT antagonist, steroids, or antihistamines

is not contraindicated in pregnancy. Granulocyte-stimulating factors are considered pregnancy category C and the use should be guided by the clinical necessity.

### ***Monitoring of Pregnancy and Delivery***

Pregnant women with breast cancer should be managed in a high-risk pregnancy clinic in collaboration with an oncologist. Gestational age should be accurately determined to aid in planning treatment and timing of delivery. Frequent clinical examinations and fetal ultrasound examination should be performed to monitor the fetal growth appropriately. An imaging study like echocardiogram of the heart to assess the cardiac function is recommended if an anthracycline-based chemotherapy regimen is to be administered to the mother.

Ideally, chemotherapy should be withheld for 3 to 4 weeks before anticipated date of delivery to prevent infectious or bleeding complications secondary to myelosuppression. Ideally, the fetus should be delivered after confirming fetal pulmonary maturity or after 34 weeks of gestation to prevent neonatal complications. The mode of delivery should be dictated by the obstetrical indication.

Lactation: patients receiving chemotherapy should be cautioned against breast feeding as many cytotoxic drugs and supportive medications are secreted in the breast milk and can result in exposure of the baby to these medications.

### ***Termination of Pregnancy***

Elective termination of pregnancy has not been shown to improve outcomes in breast cancer. Hence this is not routinely recommended. However, in early pregnancy, this option should be discussed along with the other treatment options since delaying definitive therapy until after the first trimester could adversely

affect maternal outcome. The decision to terminate the pregnancy should be individualized based on the maternal concerns and oncologic situation.

### ***Prognosis of Breast Cancer Associated With Pregnancy***

The prognosis of breast cancer occurring during pregnancy has changed over the years. Earlier reports suggest that PABC has a worse prognosis, which was perhaps largely related to the delayed diagnosis and more advanced stage at presentation. A recent report on outcome of 32 patients with PABC when matched for age, stage and other characteristics was shown to be comparable to the outcome of non-pregnant breast cancer patients.<sup>16</sup> However some older reports indicate decreased survival in pregnant women with breast cancer.<sup>1,17</sup>

### ***Follow-up After Treatment***

Women with breast cancer occurring during pregnancy should be monitored for recurrence as per guidelines recommended by the American society of Clinical Oncology and the National Comprehensive Cancer Network for all women with breast cancer. This includes comprehensive history and physical exam every 3 to 6 months for the first 3 years and every 6 to 12 months for the next 2 years. Annual mammograms should be performed. No additional imaging is necessary for surveillance.

### ***Genetic Testing***

Given the younger age of the women with PABC, the risk of carrying a mutation in a gene (such as *BRCA1* or *BRCA2*) responsible for a hereditary cancer syndrome is higher and genetic counseling and testing should be offered to all these women.

### ***Pregnancy After Breast Cancer***

The safety of pregnancy after breast cancer is an important issue as more young women with breast cancer survive longer

with effective therapies. Several population-based studies have reported that women who become pregnant after successful treatment of breast cancer do not have adverse cancer outcomes.<sup>18,19</sup> In fact there are data suggesting a favorable effect of a subsequent pregnancy on early breast cancer (suggesting a possible anti-tumor effect of pregnancy). At this time, the consensus is generally to avoid pregnancy in the immediate 2 to 3 years after treatment as there is a higher chance of recurrence in this period. However, this is based on small patient cohort studies. Moreover, a healthy mother effect may have biased the selection in these studies. In a recent meta-analysis of published studies corrected for this bias (so as to assess the effect of pregnancy (at least 10 mo after diagnosis vs. no pregnancy on overall survival), pregnancy after 10 months of diagnosis of breast cancer did not adversely affect the outcomes.<sup>20</sup>

### ***Summary***

As women delay childbirth, incidence of PABC is expected to rise. A high degree of suspicion is necessary to ensure timely investigation and diagnosis of breast cancer in a pregnant woman with a suspicious breast lump. Surgery as an initial approach is more suitable when diagnosis is made in the first trimester and systemic therapy can be delayed to second trimester. Diagnosis of breast cancer in the later stages of pregnancy can be managed with either primary chemotherapy or surgery. A multidisciplinary approach involving medical and surgical oncologists, high-risk obstetric care, genetic counselors, pharmacists, radiation oncologists, and neonatologist is highly recommended for the successful management of the cancer and pregnancy.

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