

MANAGEMENT OF BREAST CANCER IN PREGNANCY**Mizda Abdulateef Othman*¹, Lateef Shareef Sabeeh² and Khawla Ali Majeed³**

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ABSTRACT

Although breast cancer during pregnancy (BCDP) is rare (occurring with only 0.4% of all BC diagnoses in female patients aged (16–49 years), management decisions are challenging to both the patient and the multidisciplinary team. Anthracycline-based chemotherapy can be safely initiated only in the second and third trimesters. The rate of congenital abnormalities in children exposed to chemotherapy is similar to the national average (approximately 3%). Dosing of chemotherapy should be similar to that in the nonpregnant patient (i.e., actual body surface area). Antihuman epidermal growth factor receptor 2 therapy, radiation, and endocrine treatment are contraindicated in

pregnancy and lactation. Care should include a partnership with obstetricians. To maximize benefit and minimize risk to the mother and fetus, an informed discussion with the patient and her medical team should result in an individualized treatment plan, taking into account the timing of the pregnancy and the stage and subtype of the breast cancer.

KEYWORD: Breast cancer, pregnancy.

INTRODUCTION

Breast cancer is one of the most commonly encountered types of malignancy during pregnancy.^[1] Approximately 0.2% to 2.6% of all breast cancers occur during pregnancy (BCP).^[2] There was a general belief among physicians in the first half of the 20th century that

breast cancer, under the stimulus of pregnancy, was especially aggressive, and surgical treatment was pointless and thus contraindicated.^[3]

Indeed, the gestational physiologic alterations in the breast result in a later diagnosis and higher-stage tumors. A comprehensive review from 1953 showed improved survival rates for patients with breast cancer in association with pregnancy, from 0% 10-year survival before 1920 to 22.4% in the period from 1941 to 1950. The survival rates were poorer than in the nonpregnant patients, probably because of the advanced stage of disease and delay in treatment; prompt commencement of treatment was necessary to improve survival rates. Since then, surgical treatment of BCP has become commonplace, and in the last decade, chemotherapeutic treatment during the second and third trimesters of pregnancy has also been introduced and deemed unharmed to the fetus.^[4]

Breast cancer is the most common cancer diagnosed in pregnancy and postpartum, and occurs in approximately in 3,000 pregnant women. The average patient is between 32 and 38 years of age and because many women choose to delay childbearing, it is likely that the incidence of breast cancer during pregnancy will increase.^[5] patients were treated according to guidelines for nonpregnant patients, with some modifications to protect the fetus. These modifications include delaying chemotherapy until after the first trimester, avoiding trastuzumab and endocrine therapy during pregnancy, postponing radiation until after delivery, performing an axillary dissection instead of a sentinel lymph node biopsy (SNB), and holding chemotherapy 3 to 4 weeks prior to delivery.

Whether pregnancy itself negatively influences prognosis remains a subject of debate. We still have no comprehensive understanding of the interaction between pregnancy and breast cancer carcinogenesis. Some studies have shown a poorer prognosis for BCP^[6], whereas others have found similar survival rates when compared with a control group of nonpregnant patients.^[7] Up to now, reports on prognosis have had two major limitations, including small cohorts and the pooling of breast cancer diagnosed during and within 1 year after pregnancy (ie, pregnancy-associated breast cancer).

Breast cancers diagnosed during pregnancy (or up to 1-year post partum) have unfavorable clinicopathologic features, such as high tumor grade and low expression of estrogen receptor (ER) and progesterone receptor (PR), compared with breast cancers diagnosed in nonpregnant women of the same age.^[8]

However, whether or not pregnancy compromises survival remains a matter of debate. The treatment of these women is challenging because both the health of the mother and of the fetus need to be considered.^[9] Chemotherapy is not advisable during the first trimester of pregnancy; radiotherapy and hormonal therapies are not recommended at any time during pregnancy.^[10] A pregnancy that occurs more than 1 year after a diagnosis of breast cancer does not appear to affect survival.^[11] It is not clear how long a woman should wait after undergoing breast cancer treatment before attempting a pregnancy.

Most women are advised to postpone pregnancy for at least 2 years after treatment. The main reason for this recommendation is a concern that gestational hormones, in particular, estrogen, might stimulate dormant micrometastases, and thereby worsen survival.^[12] This study was conducted to compare the overall survival of women diagnosed with breast cancer during pregnancy or in the postpartum period, with that of women who had breast cancer but did not become pregnant.

OBJECTIVE

Discussion Breast cancer in pregnancy presents a challenging situation, since the welfare of both the mother and the fetus must be taken into account. Patients diagnosed with breast cancer while pregnant should receive the same treatment as nonpregnant patients with a few modifications to protect the fetus. However, the treatment should be approached with curative intent. Most of the patients in our study were treated appropriately according to recent guidelines.^[13]

The first suggested guideline is that pregnant women should not undergo chemotherapy in the first trimester. Given that the mechanism of action of most chemotherapeutic agents is to target and destroy rapidly dividing cells, it is no surprise that these agents are teratogenic. Fetal malformations can be as high as 15 to 25% in fetuses exposed to chemotherapeutic agents during the first trimester compared with 2 to 3% of fetuses with no chemotherapy exposure.

Although chemotherapy is not contraindicated in the second and third trimesters, about half of all fetuses with chemotherapeutic exposure during that time are at increased risk for intrauterine growth restriction, prematurity, and low birth weight. None of our patients received chemotherapy in the first trimester. The patient with the earliest gestational age at diagnosis was 12 weeks and she chose to terminate the pregnancy. Although pregnancy

termination may be considered during treatment planning, it has not been demonstrated to improve outcome. Treatment with trastuzumab in Her2-positive tumors is not recommended during pregnancy as it can cause oligohydramnios. Her2 is strongly expressed in fetal renal epithelium. In a study examining the effects of trastuzumab on pregnancy,^[14] fetuses were evaluated. Three had renal failure, four died, and eight had a decreased amniotic fluid volume. The surviving fetuses had the spontaneous return of renal function in utero after the drug was stopped, and the severity was linked to the duration of exposure. The patient who received trastuzumab during pregnancy in our study was induced at 33 weeks for oligohydramnios, with an amniotic fluid index of 3.4 cm. She delivered an infant who had a birth weight that was appropriate for gestational age and had a 5-minute Apgar score >. No patients in our cohort received hormonal agents such as selective estrogen receptor modulators, which can disturb the hormonal environment. Such treatment should be delayed until after birth. Tamoxifen has the potential to induce fetal harm during pregnancy and is associated with birth defects including craniofacial malformations, ambiguous genitalia, and fetal death.^[15]

Back ground

Pregnancy and breast cancer: risk versus benefit

Compared to the nulliparous peers, full-term pregnancy seems to predispose a female to a transient increase in breast cancer risk before a crossover effect after many years bestows an ultimate life time protective effect. The magnitude of this transient risk looks greater in women with advanced maternal age.^[16] Over all each year of increased maternal age at first birth results in an estimated 3.5–5.3% increase in life time relative risk for breast cancer.^[17] In terms of life time breast cancer risk, it seems that the age of 35 years acts as a critical point; prior to this age full-term pregnancy offers women some degree of protection, but after this age full-term pregnancy is associated with a permanent increase in breast cancer risk.^[18]

A pregnancy that ends with preterm delivery has less transient increased risk and less long-term protection. Suggested mechanisms for post pregnancy transient increase in breast cancer risk include high exposure of breast tissue to endogenous estradiol during pregnancy.^[19] Endogenous estradiol and its metabolites are genotoxic, mutagenic, and so carcinogenic. Multiple folliculogenesis which results from the use of clomiphene citrate or gonadotropins, understandably, results in a rapid increase in estradiol production. But the carcinogenic and

adverse prognostic potential of such a phenomenon in pregnancy associated breast cancer though reported but yet to be proved conclusively.^[20]

Most cases of breast cancer related to BRCA1 and BRCA2 are diagnosed in young women and so the collision of pregnancy and breast cancer in such mutation carriers is likely. Johansson et al. addressed such likeliness in his small sample size study and suggested careful monitoring of BRCA1 (and perhaps also BRCA2) mutation carriers during and after pregnancy.^[21]

Diagnosis and evaluation

An average delay of 5–7 months in diagnosis is accounted for by the physiologic changes induced by pregnancy in the breast.^[22] In the case of breast carcinoma with a tumor doubling time of 130 days, 6 months delay increases the risk of axillary metastasis by 5.1%.

In contrast to age-matched non-pregnant population pregnancy-associated breast cancer is detected at a higher stage. A 2.5-fold increased risk of advanced disease has been reported.^[23] Around two thirds of pregnancy associated breast cancer are diagnosed in the postpartum period and mostly in the first 6 months following delivery.

Painless breast mass is the usual presentation, reported in 80–95% of cases of pregnancy associated breast cancer. In breast feeding mothers, the infant may refuse the cancerous breast (milk rejection sign).^[24]

Ultrasonography, a simple and sensitive investigation for the evaluation of breast masses in pregnancy and lactation should replace the use of mammography in such cases. The increased breast density in pregnancy and lactation obtunds the ease of interpretation and so the sensitivity of the otherwise safe standard two view mammography. Fetal radiation exposure in a standard two view mammography is 0.004 Gy, a dose which is far less than the radiation thresh-hold dose (0.05 Gy) for teratogenicity in the most radiation sensitive phase (organogenesis phase) of fetal development.^[25] To avoid false positive diagnosis, owing to the pregnancy-related hyper proliferation of breast tissue, a coreneedle biopsy should be preferred over FNAC and pathologist should be informed about the pregnancy of the patient and should have experience with such specimens.^[26]

In palpable masses, which is the most common presentation in these patients, a core needle biopsy may be the most cost-effective initial procedure. Procedural complications in breasts

of pregnant women which specifically relate with pregnancy include milk fistula, hematoma, and wound infection. These are minimized by the use of ice packs, breast binding, prior use of bromocriptine for one-week, pre-procedural breast emptying, adequate hemostasis, and use of prophylactic antibiotics.^[27] X-ray chest and low dose bone scans which expose the fetus to the radiation doses of 0.00008 Gy and 0.0008 Gy respectively are considered safe in pregnancy.^[28]

Low dose bone scan if essential for evaluation should be done a well hydrated patient with an indwelling catheter to avoid retaining radioactivity. Nonetheless, investigations which involve the use of ionizing radiations should be used in pregnant patients only when the positivity of the investigation will change the immediate management and will be performed with proper abdominal shield irrespective of the radiation dose involved. In asymptomatic patients staging bone scan and abdominal imaging have a too low yield to be necessary. For abdominal imaging USG is preferred, computed tomography is usually avoided, and presently UK medical devices agency recommends avoiding MRI in the first trimester until further information.^[29]

Treatment options

Management of breast cancer during pregnancy earns a multidisciplinary approach involving obstetrician, surgeon, and oncologist for defining the optimal use of multimodality approach within the limitations imposed by particular trimester of pregnancy. Generally, the data for immediate treatment is reassuring, and delay or refusal to undergo therapy has serious consequences.^[30]

Although standard protocols are not available, surgery is usually the first line treatment with mastectomy and axillary clearance being preferred options while deferring the reconstruction.

Surgery

Surgery, the definitive treatment for pregnancy-associated breast cancer, seems reasonably safe. Surgery during pregnancy is fraught with increased risk for spontaneous abortion (Relative risk [RR], 1.58–2)^[31], low and very low birth weight (RR, 2.0–2.2), and infant mortality (RR, 2.1).

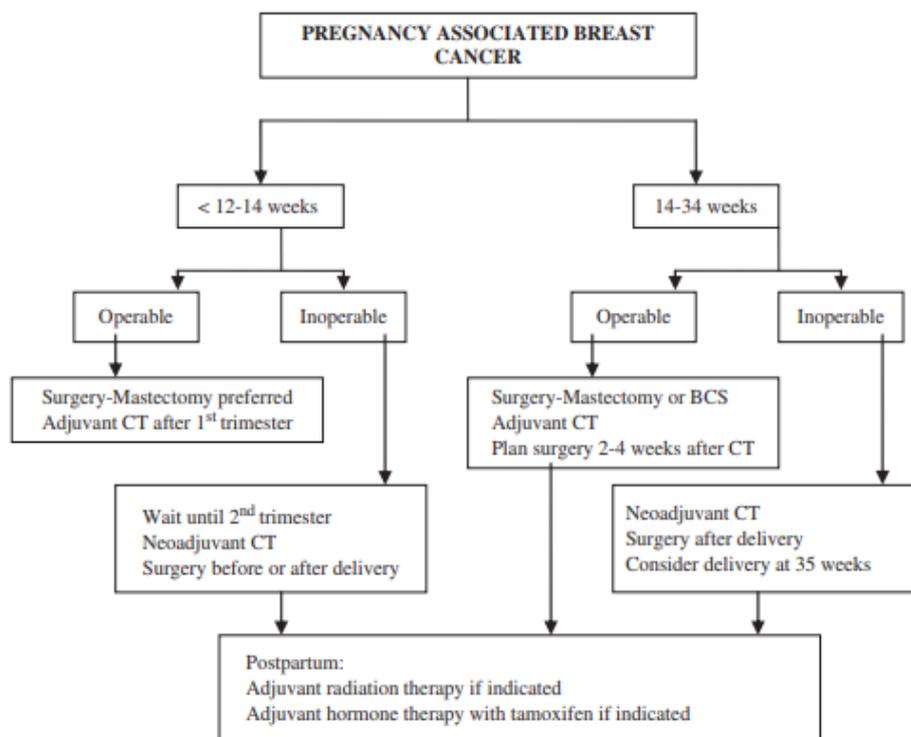
The relative contributions of anesthesia, the underlying disease for which surgery is done, and the surgery itself in the causation of such obstetric adversity and not known. It is the

radiotherapy component of breast conservation therapy which offends the use of conservative breast surgeries in pregnancy particularly in the first trimester of pregnancy. Therefore, modified radical mastectomy remains the standard management. However, the use of breast conservative surgeries can be considered in the third trimester of pregnancy when radiotherapy will be delivered after delivery. Breast conservation surgery can also be considered in the late second trimester of pregnancy in patients who are expected to receive intervening chemotherapy, which practically is the case in most of the patients in view of young age and associated bad prognostic factors till radiotherapy after delivery.^[32] Because of the significant delay in radiotherapy of more than 8 weeks is an issue only in patients who do not receive such intervening chemotherapy. An analysis has been performed that helps predict the risk of waiting to have radiation.^[33]

The spectrum of breast surgery that is reported as safe in the limited available relevant literature includes breast conservative surgery, mastectomy, and axillary dissection. Axillary clearance as expected is preferred in view of the advanced stage at presentation. The panel of the consensus conference on the role of sentinel lymph node biopsy (SLNB) in breast carcinoma had recommended against its use in pregnancy until more data will become available. Gentilini et al. in their landmark study estimated fetal radiation exposure of less than 0.05 Gy in the standard procedure of SLNB using a single peritumoral injection of ^{99m}Tc labeled human colloid particles in a volume of 0.2 ml with an average activity of 12.1 MBq, 16–18 hours before the surgical intervention. Furthermore, it was concluded in the study that SLNB for breast cancer can be performed in a pregnant patient with due consideration to certain practical aspects viz avoiding contact with other nuclear medicine patients (e. g. by scheduling pregnant patients as the first procedure of the day and keeping the patient in a single bed-room), and reducing time interval between lymphocintigraphy and surgery, with a consequent possible reduction of the administered activity. The use of isosulfan blue has not been approved by the US Food and Drug Administration (FDA) because of the risk of anaphylaxis.^[34]

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 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 cancer. A treatment algorithm is outlined in Figure 1.



Pregnancy-associated breast cancer

Most cases of PABC present as painless masses, and up to 90% of these masses (as is true of the population as a whole) are found by the patient herself.^[35] Occasionally, an infant will inexplicably refuse to nurse from a breast that is subsequently demonstrated to harbor a breast cancer, the so-called milkrejection sign.

Clearly, any breast mass warrants prompt attention, especially in a patient who is pregnant or lactating. Every effort must be made to reduce the delay between symptoms and diagnosis in PABC. A thorough breast examination should be an integral part of the initial prenatal physical examination. This should be done before the development of the physiologic breast changes enumerated earlier, which may conceal abnormalities. Delay in diagnosis may be minimized if both physician and patient are aware that breast changes may be manifestations of an underlying malignancy as well as normal alterations related to pregnancy and lactation.^[36]

An enlarging mass that persists without regression, and other primary or secondary signs of malignancy (nipple retraction; fixation of mass to skin with or without skin thickening, dimpling, or fixation to underlying tissues; development of axillary lymphadenopathy) should be taken as indications of possible malignancy, and the diagnostic workup must be prompt given any of these findings. As in the nonpregnant patient, an occasional woman with PABC has extensive metastatic disease at initial presentation (sometimes with an occult breast primary).^[37]

Methods

The research review focused on patients diagnosed with breast cancer during pregnancy.

These charts were extracted using corresponding to breast cancer (11) and pregnancy. These charts were then reviewed to determine if their cancer was diagnosed during pregnancy. Patients were included if they were diagnosed with breast cancer while pregnant. Exclusion criteria included women diagnosed with breast cancer in the postpartum period and patients diagnosed with benign breast disease. Data collected included gestational age at diagnosis, gestational age at delivery, mode of delivery, stage at initial diagnosis, imaging and/or procedure used for diagnosis, treatment, pregnancy and postpartum complications, tumor receptor status, and Breast Cancer Susceptibility Gene (BRCA) status.

RESULTS

The patients were 21 to 41 years old at the time of diagnosis, with a mean age at diagnosis of 32.9 years. Of the 11 patients, 7 were Daghdad, 2 were Baquba, 1 was Almousel, and 1 was Asian. The gestational age at diagnosis ranged from 12 to 37 weeks, with a mean gestational age at diagnosis of 25.9 weeks. Of the 11 patients, 10 chose to continue the pregnancy after diagnosis. One terminated the pregnancy at 14 weeks' gestation. Of the 10 patients who continued the pregnancy, the gestational age at delivery ranged from

33 to 39 weeks, with a mean gestational age at delivery of 36.2 years.

Of the 11 patients, 10 were diagnosed by an ultrasoundguided biopsy after an abnormal mammogram. One patient was diagnosed by a supraclavicular lymph node biopsy. One patient had stage 1 disease (9%), six patients had stage 2 (55%), one patient had stage 3 (9%), two patients had stage 4 (18%), and one patient with unknown pathology (9%).

Of the 11 patients, histology was available in 8. Of the eight patients, six had invasive ductal carcinoma (75%), one had invasive lobular carcinoma (16%), and one had inflammatory carcinoma (16%). Three patients were ER negative/PR negative (27%), one patient was ER negative/PR positive (9%), five patients were ER positive/PR positive (45%), and two patients had an unknown receptor status (18%). Her2 status was available in nine patients.

Five were Her2 amplified (55%) and four were Her2 nonamplified.

With respect to treatment, four patients received no treatment during pregnancy, four patients underwent surgery (two mastectomies, one lumpectomy, and two SNBs), and four patients received chemotherapy during pregnancy. Of the patients who received chemotherapy during pregnancy, two had surgery prior to initiating chemotherapy.

The patients who received chemotherapy during pregnancy received Adriamycin and Cytosan (two patients), Adriamycin, Cytosan, Taxol, and trastuzumab (one patient), and Cytosan, methotrexate, and 5-fluorouracil (one patient).

Of the patients who continued the pregnancy, nine patients delivered between 33 and 39 weeks.

One patient delivered at a non-Advocate hospital and her delivery information was not available. Of the nine patients with delivery information, there were three vaginal deliveries and six cesarean sections. The indication for delivery in eight of the nine deliveries was breast cancer. Only two pregnancy or postpartum complications were recorded. One patient had oligohydramnios at 33 weeks and was induced. She was receiving trastuzumab. Another patient was noted to have a postpartum neutropenic fever 8 weeks after delivery.

There was one admission to the neonatal intensive care unit (NICU) for neonatal respiratory distress. That infant was released from the NICU 2 days later. Postpartum, seven patients underwent primary or completion surgery; seven patients received chemotherapy, and three patients received radiation therapy. One patient received chemotherapy and radiation in the postpartum period. Of the patients who received chemotherapy, two received trastuzumab.

DISCUSSION

Not surprisingly, most PABC is diagnosed as a self-palpated breast mass. Most women diagnosed with BCDP are younger than age 40 years and are not undergoing routine

screening mammography. Even for those age 40 years or older, screening mammography during pregnancy is generally not recommended because of the significantly reduced sensitivity of mammography in this setting; hormone changes during pregnancy and lactation yield diffusely marked increases in breast density. Heterogeneous breast density (50% to 75% density) may obscure small masses, while extremely dense breasts (>75% density) outright reduce mammographic sensitivity. During pregnancy, there is a proliferation of glandular tissue and differentiation of secretory units in preparation for lactation.

These physiologic processes result in tenderness and an increase in breast volume and density. Such changes complicate the clinical breast exam and can delay identification of suspicious masses, resulting in more locally advanced disease at the time of diagnosis. Any breast or axillary mass that persists for longer than 2 weeks should be evaluated via diagnostic imaging and, if indicated, by biopsy. Eighty percent of breast masses identified during pregnancy are benign. The differential diagnosis of pregnancy-associated breast masses includes fibroadenoma; fibrocystic changes; galactocele; lactating adenoma; lipoma; abscess; breast cancer; and, more rarely, sarcoma, leukemia, and lymphoma.^[38]

Ultrasonography is the first line imaging modality for evaluation of a breast mass during pregnancy because it can differentiate between solid and cystic lesions and lacks ionizing radiation, which may be associated with birth defects. In several studies, ultrasonography had an extremely high sensitivity in the detection of BCDP and detected both benign and malignant lesions. Robbins *et al.* report a 100% sensitivity for ultrasonography compared with 78%–100% for mammography.^[39] Ultrasonography is generally recommended for evaluating breast lesions in women younger than age 30 years because of increased breast density in this age group. However, in the dense breast of pregnancy, ultrasonography is appropriate at all ages. Ultrasonography-guided core biopsy can be performed for tissue diagnosis. Once a malignancy has been identified or is strongly suspected, mammography is also helpful to determine the extent of disease, visualize suspicious microcalcifications, and evaluate the contralateral breast, but with the limitations discussed in the “Clinical Presentation” section. There is minimal risk to the developing fetus with mammography because of modern shielding techniques. Ionizing radiation exposure to the fetus is less than 0.03 mGy, several orders of magnitude less than the 50,000-mGy threshold above which teratogenic effects are a concern. Lead shielding reduces this risk an additional 50%,

suggesting that mammography with proper shielding presents an exceptionally low risk to the developing fetus.

To put these doses of ionizing radiation into perspective, a fetus is exposed to an average of 1,000 mGy of background radiation during normal development.^[40]

CONCLUSION

Diagnostic modalities which are used for breast cancer seems satisfying including standard two view mammogram with the abdominal shield but their long-term safety is yet to be proved. Use of surgery and chemotherapy (especially after the first trimester of pregnancy) is reasonably safe and currently modified radical mastectomy with axillary clearance followed by adjuvant chemotherapy seems the treatment of choice. Radiotherapy, as a treatment modality, is not recommended until after delivery. Pregnancy as an isolated variable does not seem to worsen the prognosis of breast cancer.

As women delay childbirth, the 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 the 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, highrisk obstetric care, genetic counselors, pharmacists, radiation oncologists, and neonatologist is highly recommended for the successful management of cancer and pregnancy.

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