REVIEW PROF-1543

PREGNANCY ASSOCIATED BREAST CANCER (PABC)

PROF. DR. M. SHUJA TAHIR
FRCS (Edin), FCPS Pak (Hon)
Professor Surgery
Independent Medical College
Faisalabad.

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ABSTRACT... Pregnancy associated breast carcinoma is an entity which is diagnosed during pregnancy or within one year postpartum. **Objective:** (1) To understand the pathogenesis of pregnancy associated breast carcinoma. (2) To be able to manage this problem most effectively in the interest of fetus & mother. (3) To be able to avoid preventable complications of treatment. **Conclusions:** The pregnancy associated breast carcinoma can be managed effectively with various treatment modalities during various stages of pregnancy & lactation. **Prognosis & outcome:** It is not worse than the stage wise carcinoma breast in non pregnant women of the same age.

Carcinoma breast is common and dreadful malignancy of the females. Women pass through various stages during their life such as infancy, childhood, menarche, adulthood, pregnancy, lactation and menopause. Women who go through pregnancy when young (before 20 years) are at the lower risk of the carcinoma breast. The women who had no children or get pregnant for the first time after 30 years of age are at two to three times higher risk[1]. Young women are lucky to have lower incidence of carcinoma breast than their older counterparts[2].

Gestational breast cancer or pregnancy associated carcinoma of the breast (PABC) is an entity which is diagnosed during pregnancy or within one year postpartum. Luckily it is uncommon but not rare. Pregnancy associated breast carcinoma (PABC) is unfortunate seen about once in 3000 pregnancies[3].

The incidence of pregnancy associated breast cancer (PABC) is likely to increase with rise in educational level and social status of professional women. More of these women are likely to choose childbearing at later age[3]. It has become an important issue because of its special nature & different treatment options.

Pregnancy associated carcinoma poses special challenge to be balanced between aggressive care for the mother with appropriate modifications that will ensure fetal protection[1]. Pregnancy related carcinoma breast presents in following situations;

- Breast carcinoma diagnosed during pregnancy
- Breast carcinoma diagnosed after pregnancy during lactation
- Pregnancy occurring in patients already being treated for carcinoma breast

There is usually delay in the diagnosis of carcinoma breast in pregnant patients due to physiological changes in the breast during pregnancy and lactation. Its diagnosis may be overlooked during pregnancy. It is because breasts are enlarged, lumpy and tender during pregnancy & lactation.

Overall menopausal status and age at menopause are significantly associated with breast cancer. Early menarche and late menopause are strong negative risk

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Correspondence Address:
Prof. Dr. M. Shuja Tahir
FRCS (Edin), FCPS Pak (Hon)
Professor Surgery
Independent Medical College
Faisalabad.
shujatahir@iu-hospital.com

factors for development of carcinoma breast. A full term pregnancy and early age at first birth are associated with decreased breast cancer risk. Post menopausal women with lactation longer than 48 months have reduced risk of breast cancer. Decreased parity, late age at first birth, early menopause and shorter duration of lactation are important risk factors[4,5].

PATHOPHYSIOLOGY

The mammary micro environment might become tumor promoting after pregnancy because of the remodeling of the mammary gland to its pre-pregnant state. The remodeling is associated with pro-inflammatory and wound healing mechanisms. It is proposed to support tumor cell dissemination[5,6].

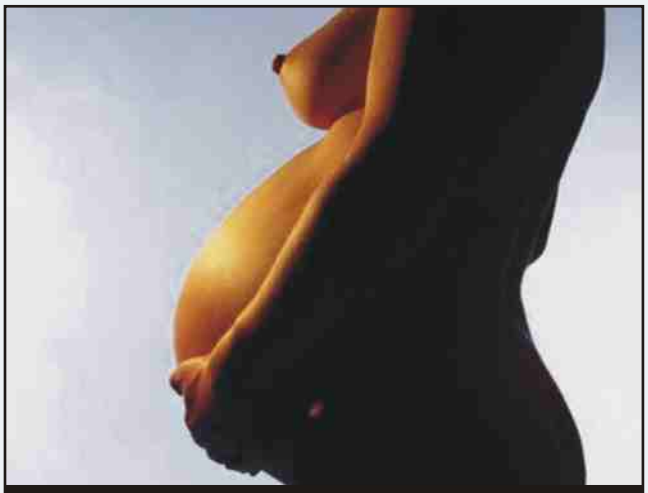

Fig-1. Suspected carcinoma breast in a pregnant woman.

Pregnancy associated breast carcinoma is predominantly invasive ductal carcinoma. Tumors are larger in size at presentation (usually II or III stage). There is frequency of lympho-vascular invasion, higher nuclear grade and hormone independence. Most of these patients are estrogen receptor negative[1].

TRIPLE ASSESSMENT

Triple assessment helps in making an accurate diagnosis which is relatively difficult in these patients.

SELF BREAST EXAMINATION

All women should be encouraged to practice breast self examination during pregnancy and lactation. Breast self examination has no effect on morbidity and mortality of carcinoma breast, but its best part is that women become aware of even minor abnormalities in their breasts and seek medical help. They get diagnosed at early stage.

CLINICAL EXAMINATION OF BREAST

The breast examination during antenatal visits may help in early detection[5]. Physicians should screen all women for cancer breast with thorough clinical examination during early pregnancy. The examination of the breast is also performed during post partum period, if patient is not breast feeding or if she presents with breast symptoms. The usual modes of presentation of pregnancy associated carcinoma breast are;

Solid mass in the breast

Solid mass may be seen in the breast of a pregnant women. Carcinoma breast is a painless, firm and deep seated mass. It may get fixed to the chest wall or overlying skin due to local infiltration. Edema of overlying skin is another feature of advancing malignancies. Axillary lymph adenopathy may also be seen in these patients.

The differential diagnosis of such a mass includes;

- Invasive carcinoma
- Lactating adenoma
- Fibro adenoma
- Cystic disease
- Lobular hyperplasia
- Galactocele
- Abscess
- Lipoma
- Hamartoma
- Leukemia (rarely)
- Lymphoma
- Sarcoma
- Neuroma
- Tuberculosis

Nipple discharge

Blood stained nipple discharge may occur during

pregnancy & lactation. It may be associated with a palpable mass or without mass. It is investigated & correct diagnosis is made histologically.

IMAGING

Ultrasound examination of breasts is performed as first line imaging examination in women with suspected breast lesions. Sonography of solid mass with posterior acoustic shadow and marked cystic component may indicate malignancy in pregnant patients[7].

Mammography is usually less helpful because of increased radio density of breast during pregnancy and lactation[7]. Mammogram may appear negative in pregnant women even though the carcinoma is present. It may show calcification, increased skin thickening & asymmetric density. Mammography of clinically obvious lumps is likely to be misinterpreted during pregnancy.

MRI examination can be performed safely as it is does not require radiation. Contrast should not be used with MRI. It can be used in selected patients with satisfactory results.

Chest X-ray is required to assess the metastatic complications in some patients. It can be used safely after proper shielding of the abdomen.

CYTOHISTOLOGICAL ASSESSMENT

FNAC or biopsy is performed to assess suspicious breast mass in a woman during pregnancy & lactation. FNAC may show incorrect results due to presence of hormonal induced atypia in these patients. Core needle/excision biopsy is performed for correct results.

Receptor status tumor receptor studies for estrogen, progesterone, and Her-2-neu receptors are performed before planning the appropriate treatment.

80% of cancer breast in pregnant women is estrogen receptor negative.

Interruption of lactation is not necessary while investigating except when radioisotope studies are conducted.

RISK ASSESSMENT CURRENT PREGNANCY AND LACTATION

The pregnancy and lactation do not increase the risk of malignancy. It is the delay in treatment of malignancy due to pregnancy which effects the outcome poorly.

Breast feeding has good effect on the prognosis of carcinoma breast. The risk for pre-menopausal breast

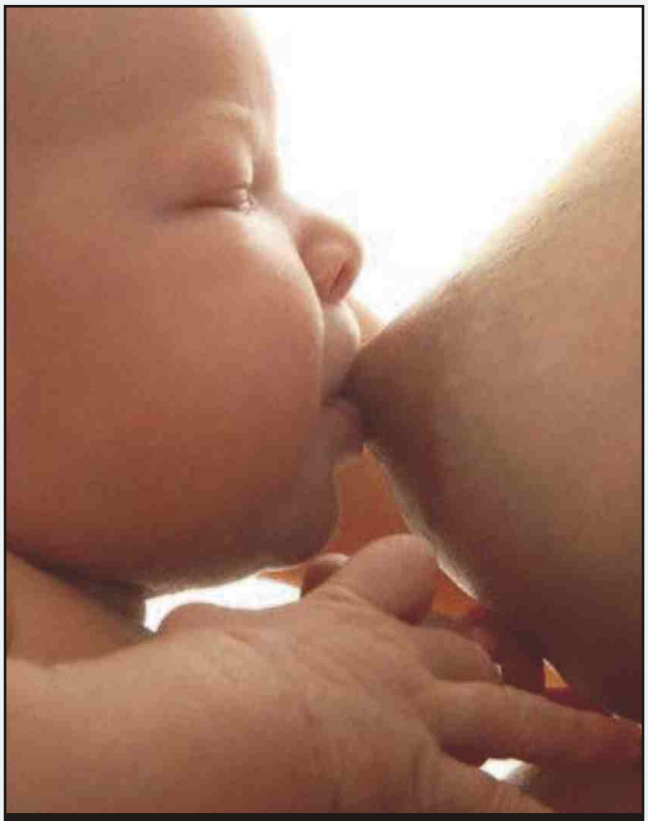

Fig-2. Suspected carcinoma breast in a lactating woman.

cancer is reduced with lactation. This protective effect is best in women with extended periods of breast feeding during their life time. Breast feeding for one and a half year to two years (1-1/2 to 2 yrs) or feeding more children is likely to lower the risk of carcinoma breast.

Women with familial risks could potentially benefit most from breast feeding. Breast milk is ideal nutrient for new born and breast feeding is a modifiable risk factor. The women should be encouraged to breast feed.

SUBSEQUENT PREGNANCY

The risk of recurrence of breast cancer during

subsequent pregnancies is not increased but pregnancy should be avoided for at least two years after successful treatment of node negative breast carcinoma. There is good evidence of chance of breast cancer in the first 3-4 years after delivery of a single baby.

GENETIC FACTORS

The pregnant women have tumors with high histological grade and low frequency of hormonal receptors and high expression of C-erb B-2[8]. Subsequently their life time risk is lower than the nulliparous women.

TERMINATION OF PREGNANCY

When cancer breast is diagnosed during early pregnancy, patient is informed about effects of therapy on fetus and on overall maternal prognosis. It has been shown by many trials that the prognosis is not altered by termination of pregnancy. It is definitely affected by delay in the required appropriate therapy.

Pregnancy may be terminated or continued as the prognosis is not affected by termination of pregnancy or keeping the pregnancy. If radiation therapy is to be given, then termination of pregnancy should be considered because of possibility of adverse effects on the fetus.

Once breast cancer is diagnosed during pregnancy or lactation or pregnancy occurs in a patient treated for cancer breast, multi-disciplinary help is used including obstetrician, surgeon, medical and radiation oncologist and breast cancer counselors.

No standardized therapeutic interventions have been reported for patients with breast cancer during pregnancy as yet. Various treatment options used presently have not been evaluated for the safety of fetus and efficacy in the mother (the patient).

SURGERY

Surgery remains the gold standard of treatment and modified radical mastectomy with axillary gland dissection is the operation of choice. Breast conserving surgery is not a preferred choice in these patients.

MANAGEMENT OF AXILLA

It is necessary to ensure correct staging and adequate definitive treatment. Axillary ultrasonography and guided FNAC helps to diagnose metastatic disease and guides in adequate axillary lymph gland dissection.

Sentinel lymph gland biopsy is controversial because of use of radio-isotopes resulting in fetal complications.

RADIOTHERAPY

Radiotherapy may be used during first trimester as the fetus is still in the pelvis and can easily be shielded. It is not used in second and third trimester because of danger of irradiation to the fetus.

Fetal radiation risks are significant during first trimester because of fetal organogenesis and least during third trimester. These include;

- Teratogenic abnormalities
- Spontaneous abortion
- Childhood neoplasia
- Haemotological disorders (leukemia)
- Abnormalities of central nervous system leading to lower IQ and mental retardation

HORMONAL THERAPY

Most of the pregnancy associated carcinoma breast are estrogen receptor negative. The use of hormonal therapy such as tamoxifen is not very helpful. Most of the infants born to women having tamoxifen are found to be normal, some of the babies had head and face birth defects.

It is recommended that tamoxifen therapy even if required should not be used until after delivery.

There is no clear evidence that hyper estrogenic state of pregnancy contributes to development of rapid growth of malignancy[1].

CHEMOTHERAPY CHEMOTHERAPY AND FERTILITY

Chemotherapy can be used in these patients with care. The patients over 30 years of age should be informed about pre-mature menopause and loss of fertility after

treatment with chemotherapeutic drugs.

Adjuvant chemotherapy should not be delayed if equired but its effects on fetus and future reproductive capabilities should be informed to and discussed with the patient.

The risks and benefits of early delivery during 3rd trimester should be compared with continuation of pregnancy. Effects of chemotherapy on fetus should be kept in mind.

Chemotherapy should not be given three to four weeks before delivery because it lowers blood count of the patients. It increases chances of bleeding and infection during and around delivery period. If patient is already receiving chemotherapy during third trimester, it should be withheld a month before delivery to avoid such complication.

The effects of treatment with high dose chemotherapy and bone marrow transplant with or without radiation therapy on later pregnancies are not known.

Chemotherapy can be used effectively during second and third trimester of pregnancy with minimal complications of labor and delivery[9]. Commonly used adjuvant chemotherapeutic agents are:

- 5 - Flurouracil 1000 mg / m^2
- Adriamycin (Doxorubicin) 50 mg / m^2
- Cyclophosphomide 500 mg / m^2

CHEMOTHERAPY AND FETAL WELL BEING

Chemotherapy has teratogenic effects on the fetus during first trimester of pregnancy. It can still be used after discussion with the patient about the risks to the fetus and mother.

These drugs are used at 3-4 weeks interval. The risk of fetal growth retardation (FGR) should be kept in mind following chemotherapy during second and third trimester of pregnancy.

PROTOCOL OF CHEMOTHERAPY

The chemotherapy is started after complete metastatic work up as given below;

- X-ray chest (with abdominal shielding in pregnancy) PA view and lateral view of both sides.
- Complete blood count.
- Renal function tests
- Liver functions tests
- Ultrasonography

Counseling is done about the risks of chemotherapy to the fetus and mother.

Central venous catheter is passed for long term use.
FAC chemotherapy is used as for following schedule.

Day One

- Injection cyclophosphamide 500 mg/m^2 intra-venously is given as a single dose.
- Injection doxorubicin 50mg/m^2 is given as continuous infusion over 72 hours.
- Injection 5 fluorouracil 500mg/m^2 is given as a bolus intravenous dose.

Day Four

- Bolus dose of injection 5 fluorouracil is given intravenously.

Three weeks onwards

This course of treatment is repeated after 21 to 28 days during second and third trimester through 37 weeks of gestation[9].

Patients are monitored with complete blood count, renal function tests and liver function tests before and during the treatment courses.

Side effects such as nausea and vomiting are treated with intravenous ondansetron hydrochloride (zafran Glaxo). Promethazene or Prochlorperazine tablets.

The fetus is looked after for fetal growth retardation

(FGR) which is common after chemotherapy.

Various modes of treatment used during different stages of pregnancy to achieve optional outcome are given below;

FIRST TRIMESTER[9]
Termination of pregnancy M.R Mastectomy Adjuvant chemotherapy
SECOND TRIMESTER[9]
M.R. Mastectomy Early delivery / section once fetus is viable Adjuvant chemotherapy
THIRD TRIMESTER
Induction of labour / section M.R. Mastectomy Adjuvant chemotherapy[9]

PREGNANCY OCCURRING IN PATIENTS ALREADY BEING TREATED FOR CARCINOMA BREAST[4,10].

Women treated for breast cancer may wish to get pregnant. Patients successfully treated for breast cancer can try pregnancy two years after the treatment but patients with advanced cancer breast should be discouraged to get pregnant. All these patients should be informed about possibility of deterioration of prognosis.

The women who get pregnant within two years of treatment of carcinoma breast require careful management.

Termination of pregnancy in these patients does not seem to improve mother's chances of survival and is not usually a treatment option. It is only considered to avoid teratogenic abnormalities in fetus. It is done with mother's consent after full counseling. It depends upon the age of fetus, stage of disease and the mother's chance of survival[3].

As the recurrence of cancer breast is common in first 2-3 years after diagnosis of cancer breast, the women should be advised to plan pregnancy after three years. These patients must have oncologic evaluation before such trial. If the patient had cancer breast with positive nodes, she should extend her pregnancy free period to five years.

The breast feeding does not increase the risk of breast cancer recurrence or development of second primary breast cancer.

PROGNOSIS

Pregnancy is no longer accepted as an independent risk for poor prognosis. The pregnant woman usually present with late stage (II or III stage disease) and lymph gland metastasis.

The prognosis of breast cancer diagnosed during pregnancy and lactation is almost similar to the stage wise carcinoma in a non pregnant women of the same age.

Overall survival is high in both node negative and node positive patients. Five and ten years survival is between 80%-86% and 73%-76%[7].

Survival In Pregnancy Associate Breast Cancer	
5years	80% - 86%
10years	73% - 76%

The pregnancy obscures the disease leading to delay in the diagnosis, hence has poor prognosis. The poor prognosis in these carcinomas is due to age and not due to pregnancy.

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