



# Pregnancy-Associated Breast Cancer: A Realistic Approach

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## Abstract

**Background** The number of cancers diagnosed during pregnancy is on the rise, and breast cancer is the most common malignancy. Presently, there are very limited resources and no clear guidelines for managing this peculiar patient population both worldwide and in India. The objective of this study was to find out the incidence of pregnancy-associated breast cancer (PABC) in a tertiary care referral centre and to compare the epidemiological, diagnostic and prognostic factors as well as maternal and foetal outcomes with the most recent literature worldwide.

**Methods** We conducted a retrospective descriptive study of women diagnosed with breast cancer in pregnancy and postpartum period at a tertiary care centre in southern India during the period of 10 years (total number of breast cancer patients were 10). We studied the diagnostic and prognostic factors as well as maternal and foetal outcome in patients diagnosed with breast cancer for the first time in pregnancy.

**Results** Overall incidence of PABC was found to be 0.6% ( $n=10$ ). Mean age at the time of presentation was  $30.7 \pm 4$  years. All cases suspected clinically or on imaging (USG) were confirmed with FNAC, excision biopsy or Trucut biopsy. Out of 10 patients, 70% ( $n=7$ ) had an advanced-stage disease on diagnosis. Histopathology suggested 90% ( $n=9$ ) had invasive ductal carcinoma and 55.5% ( $n=5$ ) had a triple negative receptor status. 20% ( $n=2$ ) of our patients had opted for a breast conservation surgery (BCS), and 70% ( $n=7$ ) of our patients underwent modified radical mastectomy with neoadjuvant or adjuvant chemotherapy/radiotherapy. One patient had a second trimester MTP in view of stage 4 disease. 77.7% ( $n=7$ ) of the nine patients who continued pregnancy underwent LSCS, out of which 57.4% ( $n=4$ ) were elective, and MRM was done concurrently with LSCS in 50% ( $n=2$ ) of the elective LSCS. The mean birth weight of the 9 neonates was  $2.2 \pm 0.5$  kg. Intrauterine growth retardation was seen in 22.2% ( $n=2$ ) neonates. 33.3% ( $n=3$ ) of the neonates required NICU support, and one baby expired on post-natal day 16.

**Conclusion** With the increasing number of elderly primigravida amongst the urban population, a clear understanding of PABC is becoming more important. A multidisciplinary team approach shall help the clinician not only in reducing the heavy burden of patient responsibility but more importantly, in guaranteeing better quality of treatment, avoiding unnecessary delays in providing interventions and providing adequate treatment.

**Keywords** Breast cancer · Pregnancy · Early diagnosis

## Introduction

Pregnancy is an altered physiological state with various challenges in myriad patient population, but nothing is as challenging as managing cancers associated with pregnancy. It causes immense physical, physiological and psychological strain on the patient and her family. The number of cancers diagnosed during pregnancy is approximately one per 1000 pregnancies [1]. Pregnancy-associated breast cancer is by definition the onset of breast cancer during the course of pregnancy or within a period of 12 months following delivery [1, 2]. Breast cancer is

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the most common malignancy diagnosed during pregnancy occurring in approximately one per 3000 pregnancies [1]. The usual age of presentation is between 26 and 49 years in most patients, with majority of the cases being diagnosed at 30–40 years of age [2]. The risk of breast cancer increases with younger age at presentation. Around 10–20% of breast cancers diagnosed in women less than 30 years occurred within 1 year of delivery [3]. According to a recently conducted Italian study, 80% of pregnancy-associated breast cancers occurred in the post-partum period [4]. Women nowadays prefer to get pregnant at a much older age than they used to previously. As the average age of pregnancy is increasing all over the world, so have the complications associated with it and the increasing incidence of cancers. Many of these patients conceive through assisted reproductive techniques and may represent a special challenge in this already complex condition. Presently, there are very limited resources and no clear guidelines for managing this peculiar patient population both worldwide and in India.

The objective of this study was to find out the incidence of pregnancy-associated breast cancer (PABC) in a tertiary care referral centre and to compare the epidemiological, diagnostic and prognostic factors as well as maternal and foetal outcomes with the most recent literature worldwide.

### Materials and Methods

We conducted a retrospective descriptive study of women diagnosed with breast cancer in pregnancy and post-partum period at a tertiary care centre in southern India during the period of 10 years from January 2008 to December 2017. A proforma having patients age, parity index, gestational age, symptoms with duration, evaluation and interventions done, HPE, mode of delivery, supportive treatment and complications that arose was considered. Neonatal outcomes including birth weight, APGAR score and neonatal complications were also noted.

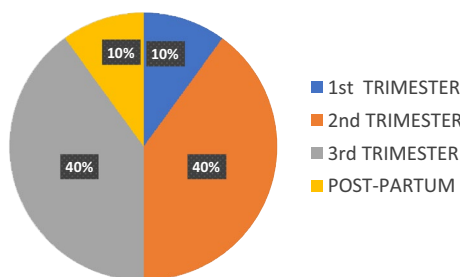


Fig. 1 Distribution of cases diagnosed

### Statistical Analysis

Numerical variables were expressed as mean and standard deviation, and categorical variables were expressed as frequency and percentages.

### Results

Overall incidence of PABC was found to be 0.6% ( $n=10$ ). Mean age at the time of presentation was  $30.7 \pm 4$  years. The mean gestational age was  $33 \pm 2$  weeks at initial diagnosis of CA breast. 50% ( $n=5$ ) were primigravidas, and 90% ( $n=9$ ) of the patients had a singleton pregnancy. Positive family history of breast cancer was present in 30% ( $n=3$ ) of patients.

90% ( $n=9$ ) of them presented with a breast lump as the first sign of their disease. The highest incidence of initial presentation was reported during the second and third trimesters (40% in each) with one case detected in the post-partum period (Fig. 1). At initial diagnosis, 30% ( $n=3$ ) of patients were classified as having stage 2 and 50% ( $n=5$ ) as stage 3 breast cancer as per American Joint Committee on Cancer (Fig. 2). As far as the histopathology report was concerned, IDC and ILC were seen in 90% ( $n=9$ ) and

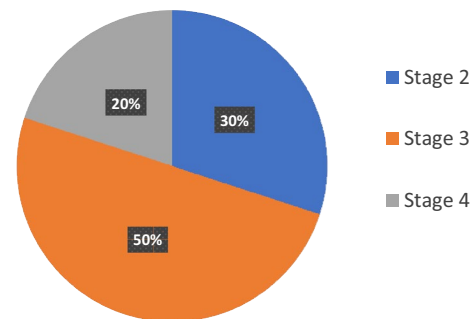


Fig. 2 Distribution with respect to stage of breast cancer (AJCC)

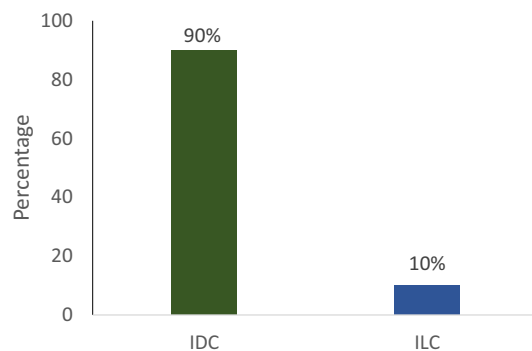


Fig. 3 Graphical distribution with respect to histopathology reports

10% ( $n = 1$ ) of our cases, respectively (Fig. 3). Hormone receptor status was available for 90% ( $n = 9$ ) of the patients in our study, out of which 55.5% ( $n = 5$ ) of patients were triple negative and the rest had positive receptor status (ER, PR, HER-2 or all).

The main modality of treatment included surgical management combined with adjuvant or neoadjuvant chemotherapy. 20% ( $n = 2$ ) of our patients had opted for a breast conservation surgery (BCS), and 70% ( $n = 7$ ) of our patients underwent modified radical mastectomy (MRM). Surgery was combined with chemotherapy (neoadjuvant/adjuvant) for all patients who underwent MRM in the antenatal period. Post-natally, radiotherapy and hormonal therapy were given depending upon the stage, histopathology and hormone receptor status. Only one patient underwent palliative therapy in view of end-stage disease with metastasis (Fig. 4).

As far as obstetric outcomes were concerned, 50% ( $n = 5$ ) women had a term pregnancy. One patient had a second trimester MTP in view of stage 4 disease. 77.7% ( $n = 7$ ) of the 9 patients that continued pregnancy underwent LSCS, out of which 57.4% ( $n = 4$ ) were elective. The most common indication for elective LSCS was iatrogenic termination of pregnancy. In 50% ( $n = 2$ ) of elective LSCS patients MRM was done concurrently. 55.5% ( $n = 5$ ) of the 9 patients opted for vaginal delivery. Out of these 60% ( $n = 3$ ) of patients were induced. However, only 22.2% ( $n = 2$ ) delivered vaginally.

When the foetal outcomes were considered, we found that the mean birth weight was  $2.2 \pm 0.5$  kg. Intrauterine growth retardation was seen in 22.2% ( $n = 2$ ) of the 9 neonates. 33.3% ( $n = 3$ ) of the neonates required NICU support mainly in view of prematurity. One baby expired on post-natal day 16.

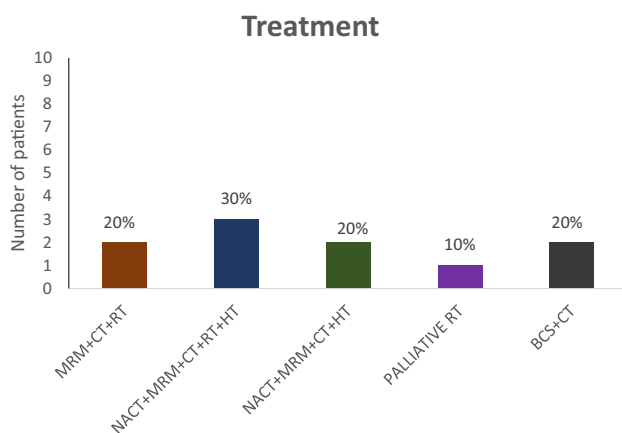


Fig. 4 Graphical distribution with respect to modality of treatment

## Discussion

Since the dawn of the twentieth century, there has been a steady decline in the recurrence rates and risk of death resulting from breast cancer due to the remarkable improvement in systemic therapy and multi-modality treatment [5]. Carcinoma of the breast is the most common malignancy associated with pregnancy, and 0.2–3.8% of diagnosis are made during pregnancy and lactation [6]. Most patients nowadays are presenting at earlier stages and proceed to live near-normal lives after completion of treatment. As a result, there is an increasing subset of patients who now wish to get pregnant in the post-treatment phase or even later. Questions related to fertility and the possibility of disease recurrence due to pregnancy are frequently asked by such patients to their doctors [7]. It has been estimated that approximately 50% of patients might wish to become pregnant subsequently [8]. But data show that only 4–7% of them manage to become pregnant. Possible reasons for low conception rates in this subset of patients include damages to fertility, lack of clear understanding of the condition on part of the physician and patient's fear of recurrence of disease condition.

In our study, the overall incidence of PABC was found to be 0.6% ( $n = 10$ ). Mean age at the time of presentation was  $30.7 \pm 4$  years. We had a total of 10 cases, and the mean gestational age was found to be 34 weeks when first diagnosed. It was found that 50% of the patients were primigravida and 90% had a singleton delivery. Contrary to the study by Gogla et al. [9], strong family history of malignancy was found in 40% of our patients, of which 30% was breast cancer.

As seen in the non-pregnant population, women with pregnancy-associated breast cancer most commonly present with palpable breast mass. Breast palpation is difficult, as the breasts of young women are firmer, more nodular and hypertrophied, particularly during pregnancy and lactation, and it is not always easy to confirm the characteristics of a malignant mass by palpation alone; breast inflammation can also be mistaken for simple puerperal mastitis. Most breast disorders related to pregnancy are benign, but given the seriousness of PABC and the risk of a delayed diagnosis, all masses during this period must be carefully evaluated [10]. It is imperative that the physician proceeds with a careful local and systemic examination as would be done in a non-pregnant woman followed by an imaging study. Most of the confusion related to diagnosis can be avoided with a thorough clinical examination. An ultrasound of the breast usually follows clinical examination and is the initial test of choice. If a patient has no abnormalities suspicious of malignancy clinically and the benign features are confirmed sonographically, then it is

safe to keep her on a short-term follow-up. But if there are any suspicious features and ultrasound is indeterminate, then it is prudent to proceed with a mammogram. In the study conducted by Langer et al., there were no PABC during pregnancy when both mammographic and US results were negative. In suspected cases of breast inflammation, not responding to appropriate medical treatment mammography should be quickly complemented by biopsy. Diagnosis is almost always delayed, and this is the most important cause for increased morbidity and mortality seen in pregnancy-associated breast cancer [10].

The gestational age of the patient and physiological alterations in the breast make clinical examination and diagnosis difficult. A delay of 1 month in diagnosis translates into a 0.9% increase in the odds of lymph node metastases. Once breast cancer is definitively diagnosed by biopsy, a mammogram of the opposite breast (with abdominal shielding) is to be done to rule out undiagnosed malignancy (foetal exposure 0.004 Gy). A roentgenogram of the chest (foetal exposure 0.0001 Gy) can be done to rule out any pulmonary metastases. An ultrasound of the liver is recommended if there is any suspicion of liver metastases. If the patient is symptomatic and metastases are highly suspected, either a skeletal survey via MRI or a modified bone scan can be performed. MRI scan of the breast is not done routinely for breast cancer during pregnancy because of two important reasons; firstly, it requires the pregnant lady to lie in a prone position. Secondly, the use of gadolinium contrast is associated with adverse foetal outcomes. However, in this study, in addition to ultrasound imaging of the breast, only one of the patients with stage 4 disease required MRI in view of her symptoms to detect vertebral metastasis. Based on the clinical examination and imaging studies, the patient is staged similar to a non-pregnant lady. In our series, 90% presented with breast lump as the first sign of the disease and the highest incidence being in the second and third trimesters (40% in each). All cases suspected clinically or by imaging (USG) were confirmed with FNAC, excision biopsy or Trucut biopsy depending upon the lesion which is consistent with the results of previous studies. Most of the patients in our study had advanced-stage disease (stage III or more as per AJCC) at initial diagnosis (70%) [9]. These results are consistent with those found in previous studies.

Similar to studies reporting that 70–90% of PABC was associated with invasive ductal carcinoma, followed by invasive lobular carcinoma, we have also found that 90% of our patients had IDC [11]. There seems to be mixed results with regard to the receptor status of patients with PABC. Few studies show a higher rate of receptor negative cancers, while others find no difference compared to non-pregnant women with breast cancer which was consistent with our study with 55.5% triple negative receptor status. As mentioned previously, the most common cause of increased

morbidity and mortality in PABC is not due to a more virulent course of this malignancy during pregnancy and parturition. The main reason is simply the delay in diagnosis and treatment. Every effort must be taken to diagnose PABC at an early stage and avoid such delays in treatment of this challenging set of patients.

Multi-modality treatment is the norm for any breast cancer patient even if she is pregnant. The main modality of treatment included surgical management combined with adjuvant or neoadjuvant chemotherapy. Mastectomy under general anaesthesia can be performed at any gestational age with minimal risk to the foetus. After 20 weeks, the patient is positioned with left lateral uterine displacement to alleviate aortocaval compression by the growing uterus. In the present era, breast cancer has been understood to be a systemic rather than a localized disease. Likewise, the surgical management of previous decades such as radical and modified radical mastectomy has either been phased out or considerably reduced in surgical practise [11]. Following early diagnosis and surgery, chemotherapy can be safely initiated during the second and third trimesters. In our institute, anthracyclines especially cyclophosphamides with or without 5-fluorouracil are the most commonly used medications. Taxanes are usually started in the post-partum period. In case anthracycline-based chemotherapy is completed very early, then it may be prudent to begin taxanes without further delay by waiting till post-partum period [12].

Considering radiation, foetal radiation exposure during pregnancy is unacceptably high with normal radiation doses. Thus, radiation is reserved for the post-partum period [2]. It has been consistently proven by various studies that compared to non-intervention any treatment has been associated with good survival [13]. Delaying treatment until after pregnancy is not associated with any survival advantage. In the current study, the main modalities of treatment included surgical management; 70% of the patients underwent MRM, while 20% had BCS. Surgery was combined with chemotherapy (neoadjuvant/adjuvant) for all patients who underwent MRM in the antenatal period. Post-natally, radiotherapy and hormonal therapy were given depending upon the stage and hormone receptor status. Only one patient had to undergo palliative therapy in view of end-stage disease with metastasis.

As far as maternal outcomes were concerned, 51% women had a term pregnancy. One patient had a second trimester MTP at 16 weeks of gestation in view of stage 4 disease. 77.7% of the 9 patients who continued pregnancy underwent LSCS, out of which 57.4% were elective. The most common indication for elective LSCS was iatrogenic termination of pregnancy in order to avoid further delay in treatment, and MRM was done concurrently with LSCS in 50% of the elective LSCS. Out of the 55.5% of the 9 patients who opted for vaginal delivery, 60% were induced. However, only 22.2% delivered vaginally.

Of all the fears in management of PABC, nothing is greater than the risks associated with foetal well-being as a result of treatment. Both the patient and the clinician need to have a clear understanding of the facts as well as the myths associated with this sensitive topic. In the review of the relevant literature, Amant et al. have performed post-natal echocardiograms on children who were exposed to anthracyclines in the second and third trimesters and found no harmful foetal cardiac effects. He performed developmental testing on 70 children exposed in utero to chemotherapy for various cancers, including those of 35 women treated for breast cancer and six exposed to taxanes. Children underwent clinical neurologic examinations and assessments of their general level of cognitive functioning (Bayley Scale of Infant Development or intelligence quotient test) [14]. Normally, the placenta takes 3 weeks to metabolize the chemotherapeutic agents and promote its excretion from the foetus [12]. Hence, administering chemotherapy after 35 weeks increases the chances of spontaneous labour and may result in foetal toxicity, so this practice is strongly discouraged. It needs to be re-enforced that there are no special indications for caesarean section with regard to PABC. Routinely, obstetric indications should be followed in such patients too. In our study, the mean birth weight was  $2.2 \pm 0.5$  kg. Intra-uterine growth retardation was seen in 22.2%, and 33.3% of the neonates required NICU support mainly in view of prematurity. One baby, delivered at 30 weeks, expired on post-natal day 16 in view of prematurity.

Breast feeding is discouraged for those patients who start or continue chemotherapy after delivery. Cyclophosphamide treatment during breast feeding is known to be associated transient neutropenia. For women who have completed chemotherapy with substantial time before delivery to allow metabolism of the drug and any active metabolites, breast-feeding should not be contraindicated from the neonatal perspective [2].

Out of the 10 patients, one was lost to follow-up. All the remaining 9 patients are currently alive and on regular follow-up. 3 of the most recently diagnosed cases underwent treatment as per their diagnosed stages.

## Conclusion

With the increasing incidence of elderly primigravida amongst the urban population, a clear understanding of PABC is very important. Lack of insight leads to delay in diagnosis and proper treatment which might ultimately prove fatal for this subgroup of patients. Unfortunately, lack of awareness and unavailability of dependable set of guidelines also lead to over zealous treatment, leading to increased rates of termination of pregnancy. It is essential that clinicians

educate themselves with this challenging condition. A multidisciplinary approach shall help the clinician not only in reducing the heavy burden of patient morbidity and mortality but more importantly, in guaranteeing better quality of treatment, avoiding unnecessary delays in providing interventions and preventing overtreatment. Probably the most vital outcome of adequate understanding amongst clinicians is that their knowledge will translate into better patient management and crystallized decision making.

## Compliance with Ethical Standards

**Conflict of interest** Pooja Ramesh, Saranya Srikumar, Vimaladhithan Mahendran, Sobha S. Nair and K. Radhamany declare that they have no conflict of interest.

**Ethical Standard** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

**Informed Consent** It is a retrospective study and data were obtained from the medical records only and Institutional ethics committee clearance was obtained prior to the conduct of the study.

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