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PREGNANCY ASSOCIATED BREAST CANCER (PABC): REPORT FROM A PERIPHERAL PRIMARY SUB CENTRE IN NORTH EAST INDIA

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ABSTRACT

Background

Pregnancy associated breast cancer (PABC) is a rare entity and defined as breast cancer diagnosed during pregnancy or one-year post-partum. There is sparse data especially from low and middle-income countries (LMIC) and merits exploration.

Methods

The study (2015 to 2020) evaluated clinicopathological characteristics, treatment patterns and outcomes of PABC.

Results

There were 10 patients, median age of 29.5 years; 4 had triple-negative disease, 3 had hormone-receptor (HR) positive and HER2 negative, 2 had HER2-positive and HR negative and 1 had triple positive disease. 8 had IDC grade III tumour's and 6 had delayed diagnosis. 2 patients were EBC, 6 patients were LABC and 2 patients were MBC. Trastuzumab, tamoxifen, and radiotherapy were administered post-delivery.

Of the 10 patients, 7 were diagnosed antepartum (AP) and 3 had termination, 1 had preterm and 3 had full-term deliveries(FTDs). Among 3 patients who underwent MTP 2 patients had metastatic disease and 1 patients underwent termination willingly. Among postpartum group (n= 3), all were LABC and underwent NACT.

Conclusion

Data from the tertiary cancer centre in North east India showed that the majority had delayed diagnosis and aggressive features(TNBC, higher grade). Treatment was feasible in majority and with favourable maternal and foetal outcomes.

Keywords: Pregnancy associated Breast cancer(PABC), triple negative breast cancer (TNBC), hormone receptor (HR), HER 2, Invasive ductal carcinoma(IDC), Early Breast Cancer (EBC), Locally Advanced Breast Cancer (LABC), MBC- Metastatic Breast Cancer, Antepartum, Postpartum, MTP – Medical Termination of Pregnancy, FTD, NACT- Neo Adjuvant Chemo Therapy, BCS- Breast Conserving Surgery, MRM – Modified Radical Mastectomy.

INTRODUCTION

PABC is most commonly defined as breast cancer diagnosed during pregnancy (BCP) or one-year post-partum (BCPP). Young females with carcinoma breast have a higher predisposition to familial cancer and tend to present with advanced stage, aggressive disease biology and poor outcomes. This is even though pregnancy and breastfeeding are considered protective for the development of breast cancer [1]. In current scenarios, women are delaying childbearing for personal and/or professional reasons, which may have led to an increased incidence and reporting of PABC. Breast cancer (1 in 3000) followed by cervical cancer and melanoma are among the top 3 cancers diagnosed in pregnant women [2]. Breast parenchyma undergoes proliferation and structural changes during pregnancy and have been hypothesized to be the reason for PABCs [3]. There is sparse and often conflicting data on PABC outcomes reporting worse, similar, and even favorable outcomes [4].

Inadequate distribution and access to health care facilities, increased prevalence of infectious diseases, sociocultural practices along with reduced spending on women's health contribute to higher maternal and infant mortality in India compared to those in the developed countries [5]. Providing cancer care to a pregnant woman with equal emphasis on fetal health is a daunting task. Additionally, lack of cancer awareness, limited expertise and resources lead to delayed diagnosis. Therefore, this study aimed to analyze the PABC cases at a tertiary cancer referral Centre in Northeast India and to analyze the clinicopathological characteristics, treatment modalities as well as maternal and fetal outcomes.

MATERIALS & METHODS

A retrospective study conducted from Jan 2015 to Dec 2020 of the reproductive age group women, diagnosed with BCP or BCPP. Self-reported information by the study participants was collected periodically and passively from the electronic medical records and case files. Pregnancy associated outcomes, the treatment related outcomes and the factors affecting either of them were analyzed. Delay in diagnosis was defined as 3 months from the detection of first symptom by the patient.

Statistical analysis

Descriptive statistics were used for reporting the patient, tumor, and treatment related characteristics. For the categorical variables, the difference in proportions was tested using the Chi-square test or Fisher's exact test. We performed univariate analysis to evaluate factors affecting the outcomes and those factors that were significant on univariate analysis were used in the multivariate cox regression model. All p-values were two-sided and with an alpha of 0.05.

RESULTS

Study population

The patient, disease stage, grade, receptor status-wise distribution and treatment related parameters are provided Table 1. The cohort included 10 patients diagnosed with PABC: both antepartum (n=7) and postpartum (n=3). 4 females were multiparous, and the median age was 29.5 years [interquartile range (IQR): 21-41 years]. After first detecting a breast lump, a median of 4 (IQR: 2-10) months elapsed before attaining the histological diagnosis of malignancy where 6 patients had 3 months of avoidable delay in diagnosis. Notably, majority 71% of the antepartum patients had extremely dense breast parenchyma on ultrasonography with irregular masses that appeared to be of equal density as the parenchyma without micro-calcifications and imposed diagnostic dilemma and add to delay in diagnosis. 3 patients had positive family history of breast cancer in first degree relatives but in these patients genetic testing records could not be retrieved. There was a history of infertility treatment in three patients and use of oral contraceptives in two patients.

Table 1: Baseline characteristics

Variable	**Frequency n=10**
Median age	29.5 years (21-41)
Antepartum (BCP)	7
Postpartum (BCPP)	3
Multiparity	4
Family history	3
Median duration of symptoms	4 (2-10 months)
Delayed diagnosis	6
Laterality	
Right	6
Left	4
Trimester	
1st (0-12 weeks)	0
2nd (12-24 weeks)	5
3rd (24-36 weeks)	2
Disease Characteristics	
TNBC	4
Her2 positive and HR negative	2
Her2 and HR positive (Triple positive)	1
Her2 negative and HR positive	3
Stage	
EBC	2
LABC	6
MBC	2
Grade III	8
Treatment characteristics	
Systemic Therapy	
Anthracyclines + Taxanes	5
Trastuzumab	Curative: 1 Palliative: 2
Hormonal therapy alone	Curative: 2 Palliative: 1
Surgery	
Mastectomy	7
Breast Conservation Surgery	1
Locoregional RT	7

Oncological treatments

Systemic therapy

Among the 8 non-metastatic patients, 6 patients received neoadjuvant (NACT) while 2 patients received adjuvant chemotherapy (ACT) after surgery whereas 2 metastatic patients received some form of chemotherapy after MTP in 2nd trimester. In antepartum group, chemotherapy was continued till 35-37 weeks or two weeks before a planned delivery to minimize chances of maternal and/or neonatal myelosuppression/septicaemia. Chemotherapy related toxicity was noticed in form of febrile neutropenia (n=1), mucositis (n=2), and 2 patients with diarrhoea and hyponatremia. 1 patient with EBC had to undergo therapeutic preterm delivery at 34 weeks due to onset of preterm labour during mastectomy. Dose reductions (up to 75%) were required in three patients. There was no chemotherapy-induced death.

Loco-regional therapy

7 patients underwent mastectomy, and 1 patient underwent BCS. Women underwent surgery during pregnancy (n=2) for EBC with appropriate precautions to avoid uterine hypoperfusion, maternal hypotension, hypoxia, hypoglycemia, pain, fever, and infection and thrombotic prophylaxis was used as appropriate. Adjuvant radiation therapy (RT) was delivered to the patients (n=7) only post-partum. The details of the treatments grouped by the antepartum and postpartum cohort is given in Fig. 1A.

PREGNANCY OUTCOMES	ANTEPARTUM=7	POSTPARTUM=3
MTP	3	0
PRETERM	1	0
FULL TERM	3	3
AVERAGE BIRTH WEIGHT	1.95 KGS	2.85 KGS
STAGE		
EBC	2	0
LABC	3	3
MBC	2	0
TREATMENT DETAILS		
MASTECTOMY	5	2
BCS	0	1
CHT	7	3
TRASTUZUMAB	2	1
LRRT	4	3

Pregnancy related details

Among the 7 antepartum patients none were diagnosed during the first, 5 during the second and 2 during the third trimester. 3 patients opted for medical termination of pregnancies (MTP); among them 2 patients had metastatic disease. There were 4 live births including 3 full term, and 1 preterm delivery with average birthweight of 1.95 Kgs. One preterm baby required ventilatory support immediately postpartum for 2 weeks. None of the babies had neurocognitive decline. Within the post-partum cohort two babies were alive and attaining normal milestones whereas 1 baby died of unknown cause.

DISCUSSION

As per our knowledge this is the first study regarding PABC in our institute providing insight on the uncommon presentation of breast cancer in pregnant women or those who got diagnosed within a year of postpartum. This study was thought to be necessary to systematically study the incidence, patterns of presentation, tumour and treatment related details and outcomes of both the patients and their babies. The exact incidence of PABC in India is not known due to under reporting and absence

of national PABC registry till now. The median age at diagnosis in our study was 29.5 years which is similar to the published literature [6]. For majority of these women, this was their first pregnancy (excluding delayed childbearing as the likely aetiology) which is not in alignment with the published data suggesting that the average age at first childbirth in India is still around 20 years of age [7-9]. There was a delay in establishing the cancer diagnosis (median 4 months) since first noticing a lump and is similar to the observations made by other PABC studies reporting delays between 1 and 13 months [10,11]. Lack of awareness about breast cancer in young, reluctance to seek medical attention, inexperienced obstetrician or midwife, compounded by reduced sensitivity of clinical or self-breast examination and difficulty in detecting a breast lump due to pregnancy and lactation related changes in breast on mammography and denial are among the few reasons for the delay [12-14].

Unlike our study and that by Johansson et al., Hou et al. found a correlation between a positive family history and PABC which could be due to the differences in the PABC definition and geo-ethnic and racial differences of the cohorts [15,16].

The tumor-related characteristics like the grade and the receptor status distribution (higher proportion of TNBCs) are higher compared to the other series indicating association of PABC with aggressive biology [13]. This could also be explained by the fact that in India breast cancer occurs a decade earlier and the TNBC and HER2-neu positivity rates are higher even in the non- pregnant women than in the west [17].

The systemic anti-cancer drugs are teratogenic and are contraindicated for use during the 1st trimester [8,9]. In second and third trimester, anthracycline-based regimen have been shown to be safe without increase in perinatal deaths. There is limited data about the safety of taxanes with some older series showed increased birth complications but not hampering with infant growth [18]. Chemotherapy-induced toxicities were similar to the other reported study [19]. Trastuzumab, tamoxifen and radiotherapy all agents known to cause teratogenic effects antepartum were used in post-partum setting only wherever indicated [5].

In our study 3 underwent MTP, mostly in the 2nd trimester. 2 of them were diagnosed with metastatic disease which may have influenced their decision. For most aggressive biology, poor prognostic cancers diagnosed in the first or early second trimester, various international guidelines suggest opting for MTP, so that standard treatment can be delivered without delay to optimize oncological outcomes [8]. Luminal-A subtype of disease, early stage and precious pregnancy are few clinical situations where pregnancy should be continued if the patient and the father desire. Conception and pregnancy following successful treatment of breast cancer is possible despite the use of alkylating agents and breast radiotherapy and should be informed to all women diagnosed with advanced cancer prior to completing 20 weeks of gestation.

Our study showed no incidence of birth complications and impaired cognitive development in children born in antepartum cohort (1/7 child with preterm delivery); this is in contrast to other studies wherein morbidities and cognitive development were found to be related with each added month to delivery rather than chemotherapy cycles [10,19]. The birth weight was significantly lower in antepartum cohort which might be related to the fetus' exposure to chemotherapy. While there are studies with similar finding there are other studies also that suggest no impact on birthweight [20]. This could be also be attributed to the over-cautious attitude of obstetricians and tendency to deliver the fetus preterm in woman with PABC without any pressing medical indication. Morbidity and mortality in newborn babies are directly related to gestational age at delivery, hence, utmost care should be exercised while taking these decisions [21-23].

LIMITATIONS

The nonrandomized, nature of the study with small patient numbers introduce some bias. However, due to its uncommon presentation, conducting randomized studies may not be possible. Since some information was based on self-reporting, the education levels can have impact on the integrity of that data. Majority of the patients had aggressive biology (TNBC and higher grades) and delayed diagnosis. The treatments for breast cancer in women pregnant or otherwise are similar, with a few differences governed by the balance of oncologic versus obstetric outcome and decisions are

generally trimester dependent. Treatment was feasible in the majority of patients. Long-term effects of chemotherapy on cognitive and other milestone development needs exploration in larger prospective cohorts and collaborations.

CONCLUSION

PABC is a rare condition that is increasing in incidence possibly due to women choosing to delay childbearing and in conjuction with an overall increase in breast cancer. Experiencing breast cancer during pregnancy or lactation is a challenge both for the mother and for the practitioners involved. Data from the tertiary cancer centre in North east India showed that the majority had delayed diagnosis and aggressive features (TNBC, higher grade). Treatment was feasible in majority and with favourable maternal and foetal outcomes.

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