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PREGNANCY ASSOCIATED BREAST CANCER : DEMOGRAPHICS AND OUTCOME ANALYSIS FROM A LOWER AND MIDDLE INCOME COUNTRY (LMIC)

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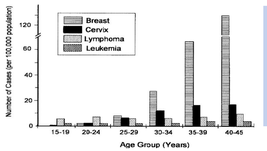
BACKGROUND

Pregnancy Associated Breast Cancer (PABC):
Defined as breast cancer diagnosed during pregnancy or one year post-partum



Berry DL et al, JCO 1999

- **Unique challenge to safeguard oncologic outcome and fetal safety**
- **Rare: 1/3000 pregnancies, 5-10% breast cancer < 40 years age**

RATIONALE

- Breast Cancer is a hormonally driven tumor
- Breast Cancer in Young and especially in pregnancy exhibits distinct biological features and an aggressive phenotype
- Sparse and inconclusive literature about PABC with variable outcomes
- Maternal and perinatal mortality in India has vastly improved -still high

In background of above setting, reporting PABC becomes all the more important

AIM /OBJECTIVES

The objective of this study was to:

Analyze PABC registry established in a tertiary care referral centre in India

To compare maternal and foetal outcomes with the published literature

To compare the epidemiological, diagnostic and prognostic factors with the published literature

METHODS

Design:
Ambispective study
Study Period:
From February2016- January 2020
Centers:
Tata Memorial Cancer Centre, Mumbai
Wadia Maternity Hospital ,Mumbai, India.

ELIGIBILITY CRITERIA

Inclusion Criteria:
- Reproductive age group women,
- Breast cancer in pregnancy and within one-year post-partum period.

Exclusion Criteria:
- Non-Pregnancy associated breast cancer
- Incomplete records missing vital information on association with pregnancy

STATISTICAL ANALYSIS

- SPSS Version 25 was used for analysis of data
- Descriptive statistics related to demographic and clinical characteristics were calculated
- For each categorical characteristic, difference in proportions was tested using the Chi-square test or Fisher's exact test
- We performed univariate analysis to see factor affecting outcome
- Multivariate Cox regression analysis was carried out with the factors found significant in univariate analysis to identify independent predictors.
- All p values were two sided and with an alpha of 0.05

STATISTICAL ANALYSIS

Survival Analysis:
- Survival Statistics: calculated by Kaplan Meier analysis and tested using log rank test
- Overall Survival (OS):Date of diagnosis with PABC to last follow-up date or date of death (where applicable)
- Event Free Survival (EFS):Date of diagnosis with PABC to any event (relapse/death due to any cause)

RESULTS

- Cohort Included 104 Patients
  34 diagnosed during pregnancy
  70 diagnosed postpartum
- Median Age: **31 (22-42) years**
- 77(74%)Patients had delayed diagnosis: **with median time to diagnosis from symptom detection was 6 months**
- Family History: **25 patients had family history**
- BRCA Mutation: **1 patient positive (185DelAG)**

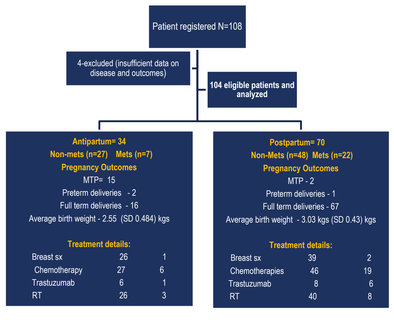
Table1:Baseline Characteristics

Variable	Frequency n (%)
Med age (range) in years	31 (22 - 42)
Antepartum Cohort	34 (32.7)
Postpartum cohort	70 (67.3)
Multiparous	93 (92%)
Family history	25 (24)
Delayed diagnosis	77(74%)
Biological Characteristics	
TNBC	43 (41.3)
Her2 positive and HR negative	14 (13.5)
Her2 and HR positive (Triple positive)	16 (15.4)
Her2 negative and HR positive	31 (29.8)
Stage	
EBC	24 (23.1)
LABC	51 (49)
MBC	29 (27.9)
Median week of pregnancy [IQR]	14 [6.15 - 24]

Variable	Frequency n (%)
Trimester	
1 to 12week	36 (61)
>12 to <24	16 (27.1)
>24 to <36	7 (11)
Missing	45
ECOG PS	
0	59 (56.7)
1	41 (39.4)
>=2	4 (3.9)
Median BMI [IQR]	24 [21 - 28]
Clinical Symptom	
Right	53 (51)
Left	51 (49)
Median duration of symptoms [IQR]	6 [3 - 12]

Treatment Characteristics	
Systemic Therapy	
Taxanes+Anthracyclines	69
Anthracyclines alone	12
Taxanes Alone	10
Taxanes+Carboplatin	4
Hormonal Therapy Alone	4
Trastuzumab received (n=21 out of 30 eligible)	15(EBC &LABC): 12 weeks (n=9) ; 1year (n=6) 6 (MBC) : palliative intent trastuzumab
Surgery (n=65; 68 breast surgeries)	
Mastectomy	27
Breast Conserving Surgery	39
Breast Reconstruction	2
Locoregional Radiation Received	77 (74)

Figure 1: Patients Profile



SURVIVAL STATISTICS

Median Follow Up = 27(19-35) Months

Criteria	Overall Cohort	EBC Patients	LABC	MBC
3 Years OS (%)	**67.8%** 95% CI: 56.5% - 81.3%	**100%**	**65%**	**46.2%**
3 Years EFS (%)	**53.4%** 95% CI 42.6% - 66.8%	**82%**	**56%**	**24%**
Mean OS (Months)		**57** 54-60 months	**48** 40 -56 months	
Mean EFS (Months)		51 44 -58 Months	43 34 -52 months	
Median OS (Months)		Median Not Reached	Median Not Reached	32 22 – 42 months
Median EFS (Months)				17 5 -30 months

FIG 2A : OVERALL COHORT
Overall Survival and Event Free Survival (N=104)

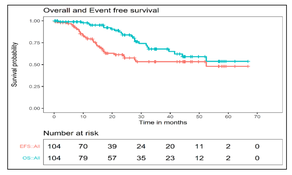


FIG 3 B:NON- METASTATIC COHORT :OS
With Respect to Disease extent (N=75)

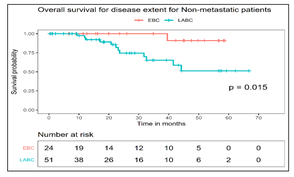


FIG 2B: OVERALL COHORT – OS
With respect to Disease Extent (N=104)

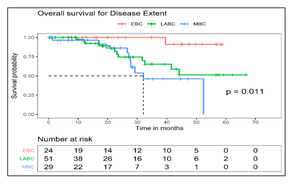


FIG 3C: NON- METASTATIC COHORT – EFS
Disease extent (N=75)

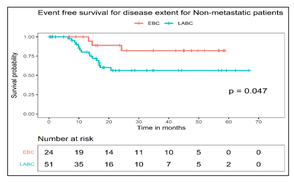


FIG 3A: OVERALL COHORT : EVENT FREE SURVIVAL
With Respect to Disease Extent (104)

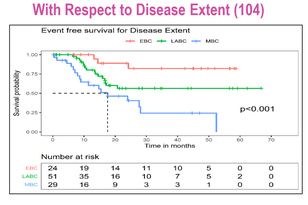


Table 2A: Factors Significant in Univariate Analysis for OS

Factors significant		Overall population [HR(95%CI), p=]	Non-metastatic [HR(95%CI), p=]	Metastatic [HR(95%CI), p=]	Antepartum [HR(95%CI), p=]	Postpartum [HR(95%CI), p=]
Disease Extent	EBC (Ref.)					
	LABC	8.35 [1.08-64.43]; p=0.04	8.43 [1.09-65.27]; p=0.04	NA	6.85 [0.80-58.36]; p=0.08	2.14 [0.46-9.94]; p=0.33
	MBC	13.03 [1.65-103.07]; p=0.02		NA	4.32 [0.38-49.64]; p=0.24	6.91 [1.55-30.74]; p=0.01
Metastasis	Yes (Ref.)					
	No	0.42 [0.18-0.96]; p=0.04	NA	NA	0.91 [0.19-4.49]; p=0.91	0.29 [0.10-0.84]; p=0.02
Radiation therapy	Yes (Ref.)					
	No	3.5 [1.46-8.30]; p=0.005	2.56 [0.33-19.89]; p=0.37	2.64 [0.65-10.75]; p=0.18	2.17 [0.45-10.58]; p=0.34	4.09 [1.39-12.07]; p=0.01
Week of pregnancy		1.11 [1.02-1.20]; p=0.02	1.17 [1.04-1.32]; p=0.01	0.38 [0.03-5.72]; p=0.48	1.12 [1.02-1.23]; p=0.02	NA*

NA – Not Applicable
NA* - Multivariate could be not be done due to less numbers

Table 3: factors significant in Multivariate analysis

		Overall Survival overall cohort				Event Free survival in postpartum cohort			
		Exp(B)	95.0% CI for Exp(B)		Sig.	Exp(B)	95.0% CI for Exp(B)		Sig.
			Lower	Upper			Lower	Upper	
Disease extent	EBC (Ref.)								
	LABC	7.793	1.007	60.310	0.049	2.104	0.454	9.767	0.342
	MBC	8.066	0.912	71.310	0.06	5.191	1.031	26.136	0.046
Radiation therapy	Yes (Ref.)								
	No	0.4159	0.146	1.184	0.1	0.588	0.2078	1.668	0.319

NA – Not Applicable
NA* - Multivariate could be not be done due to less numbers

DISCUSSION

- The median age at diagnosis in our study was 31 years, women between ages 35 to 45 have reduced fertility and might shift the median age of pregnancy to under 35 years
- 101 (97%) of tumors were IDC grade III, high proportion of TNBC (40%) and Her2-positives (30%) which connotes a biologically aggressive disease; this is in sync with Indian breast cancer characteristics
- Of the 104 patients, 77(74%) had delayed diagnosis; this reinforces the importance of educating pregnant women and care providers on the risk of PABC as well as stressing the use of self- and clinical breast exams and prompt diagnosis and treatment.
- Only a third of the women diagnosed during pregnancy like other series , this might be due to the diagnostic delays.
- Historically pregnancy and breast feeding are considered a protective factors in reducing the risk of breast and ovarian cancer. However, the hyper-hormonal state of pregnancy causing a a second hit and importance of oxytocic molecular signatures contributing for PABC is an active area of research
- Approximately one in two underwent MTP, mostly in the 1st trimester [A third of them were diagnosed with metastatic disease] ; guidelines support this option in aggressive disease and poor prognostic cohort in a multidisciplinary setting involving parents
- Luminal A subtype of disease, early stage at presentation and precious pregnancy are few clinical situations where pregnancy should be continued if the patient desires.
- Majority (88) of our patients were treated with anthracyclines & taxanes which are safer options
- Morbidity and mortality in newborn babies is directly related to gestational age at delivery, which is an important clinical message because the decision to deliver the fetus preterm is often taken without pressing medical indication
- Since the pregnancy with cancer is essentially unknown territory, there is need of further research to determine the safety of diagnostic and therapeutic procedures

OUTCOME COMPARISONS

Survival in our cohort wherein at a median follow up of 27(19-35) months, 3 years predicted EFS in EBC, LABC and MBC patients were 83% 62% and 15% respectively and is comparable to other cohorts.

Study	Pregnant	Non Pregnant	death/recurrence
Azim et al (2013)	333	874	reduced
Cordoba et al (2011)	18	97	reduced
Azim et al (2011) – M/A	1244	18145	reduced
Valachis et al (2010) – M/A	1089	13051	reduced
Ives et al(2007)	123	2416	reduced
Kroman et al (2008)	371	9865	reduced
Blakely et al (2004)	47	323	No difference
Mueller et al (2003)	438	2775	reduced
Gelber et al (2001)	94	188	reduced

LIMITATIONS

- **The nonrandomized, ambispective nature of the study with inherent bias associated with retrospective component is there**
- However, **this kind of study can never be randomized** and meaningful inferences can be obtained by prospective and retrospective cohort studies in this kind of rare situations
- There is a possibility of interpretation variation based on education level, which might affect patients self-reporting.
- However, we confirmed the patient history with medical records for this data set which greatly reduced the chances of bias.

CONCLUSIONS

- This is the data from first registry on PABC from India from a large tertiary cancer care centre
- The treatments for breast cancer in women pregnant or otherwise are similar, with a few differences governed by the balance of maternal versus fetal health, and oncologic versus obstetric outcome
- The treatment recommendations should be discussed in a multidisciplinary meeting and are generally trimester-dependent ;age at diagnosis, parity and existing fertility issues are important factors in informed decision making
- The stage matched outcomes are comparable . Long term effects of chemotherapy on cognitive and intellectual milestones need to be evaluated in a prospective manner.
- Guidelines with regards to PABC is still evolving, hence collaborative national and international registry with long term follow up data is of paramount importance to optimize outcomes at national level as well as globally

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DISCLOSURE INFORMATION
No Personal Financial disclosures to declare