The Prognosis of Patients with Pregnancy Associated Breast cancer: Retrospective Cohort Study.

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ABSTRACT

Background: Pregnancy associated breast cancer (PABC), diagnosed during pregnancy or one year post-partum, is relatively rare disease and surrounded by controversies about its prognosis and outcome. **Methods:** This cohort study is a review of retrospectively collected data of patients diagnosed and treated as PABC from 1987 to 2012 at the Aga Khan University Hospital, Pakistan. We identified patients of PABC and compared with non PABC patients matched for age and stage accrued at 1:2 ratios. The outcomes i.e. Overall survival and Disease Free Survival (DFS) were analyzed with Kaplan Meir Curves and Cox Proportional Hazards regression adjusted for matching. **Results:** We identified 62 patients of PABC, who had more aggressive disease (higher grade and receptor negativity) with higher number of patients who underwent mastectomy. Median overall survival in PABC group was 2.4 years (range: 4 months-8 years) compared to 5.5 years (range: 1.7 years-14 years.) in non PABC group (p-value 0.001). Similarly, the cases with PABC showed inferior DFS (median 1.5yrs) as compared to non PABC (median 3.2 yrs) (p-value= 0.01).**Conclusion:** PABC has aggressive course with a poor survival as compared to non PABC cases.

Key Words: Pregnancy, Breast cancer, Overall survival, Disease Free Survival

INTRODUCTION

Cancers diagnosed during pregnancy or within 12 months of delivery are called pregnancy associated breast cancers (PABC) and Breast cancer is the most common cancer diagnosed in pregnancy.[1,2] The incidence of PABC is reported to affect between one in 3000 to 10,000 pregnancies.[3-5] Around 10,000 new cases of PABC occur every year worldwide.[6] The precise incidence of PABC in developing countries is unknown.

Diagnosis of breast cancer during pregnancy is a challenging both for the clinician and the patient. The patients and physicians may wrongly attribute cancer related symptoms to the physiological changes of pregnancy which may lead to inappropriate counselling, false reassurance, and delay in diagnosis when such symptoms are present.[7,8]

Standard treatment decisions may not be possible in PABC and potentially endanger the course of pregnancy and the fetal outcome.[9] Therapeutic abortion is needed sometimes knowing it will not improve the clinical results.

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It may also be unacceptable sometimes because of social & religious reasons thus leading to much delay in initiation of therapy as treatments themselves may presumed to be fetotoxic.[10]

The influence of concomitant or recent pregnancy on prognosis of PABC is complex. Poor prognosis is often attributed to delayed diagnosis as its presents at an advanced stage often with nodal involvement.[10]

Often aggressive tumour biology also contributes to a poor prognosis. Complex patterns of enrichment and hormonal regulation of genes in PABC suggested a distinct biological nature and aggressiveness of the disease.[11]

The prognosis of PABC has been addressed in several studies in the last decade. These studies are retrospectives reviews showing varying results. The inherent limitations of these studies include; limited information regarding tumour characteristics, biology of disease, treatments given, and small sample size with a poor matching of cases with controls.[8,12-15]

The relative rarity of PABC precludes large prospective controlled trials to be conducted to study concrete outcomes. The aim of this study was to determine the prognosis of patients with PABC vs. non PABC controls in terms of the overall survival and disease free survival in our setting. To the best of our knowledge this is the first study from Pakistan addressing pregnancy associated breast cancer. The study was approved by the Departmental research committee and Ethics research committee (3370-Sur-ERC-14).

MATERIAL & METHODS

This retrospective matched cohort study was conducted at department of surgery (section of Breast surgery) at The Aga Khan University hospital, Karachi, Pakistan. We included patients of PABC diagnosed & treated at from 1987 to 2012. We excluded patients who were lost to follow up during treatment. PABC is defined as breast cancer diagnosed during pregnancy or one year post-partum. Non- PABC was defined as breast cancer not fulfilling above mentioned criterion. We identified two Non- PABC controls for each individual PABC matched for age and stage.

The final decision regarding a treatment strategy including termination of pregnancy was based on discussions between patients & clinicians and a consensus reached in multi-disciplinary meetings. All patients were staged according to AJCC standards. All patients received definitive local treatment with Breast conservation surgery or mastectomy with or without radiotherapy & standard chemotherapy. In the first trimester chemotherapy was administered if needed after the termination of pregnancy. Adjuvant hormonal therapy & adjuvant Transtuzumab was started after delivery.

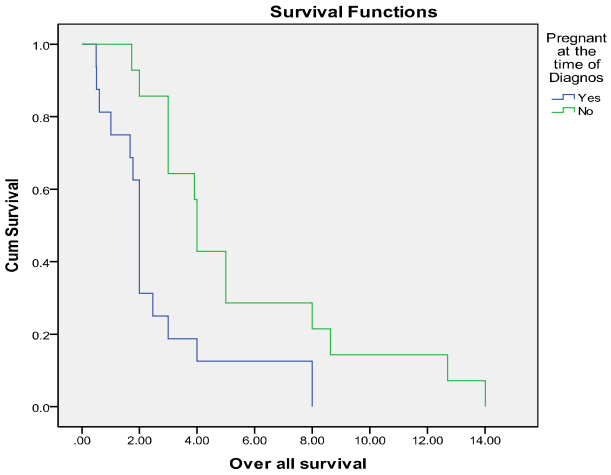

Figure 1: Overall Survival (OS) Median overall survival in PABC group was 2.4 years compare with 5.5 years in non PABC group (P value 0.001).

All pathology reports of patients were reviewed including the ER/PR & Her-2/ neu status. Data was collected for T size, nodal status, and grade, type of tumor and margin status. The ER/PR & Her-2/neu were evaluated by immune histochemistry. Her-2 neu testing was taken as standard test in breast cancer cases since 2006. Tumours scored Her-2/ neu 3+ were considered over expressing Her-2/neu. Fluorescent in situ hybridization (FISH) was undertaken for tumours expressing Her-2 neu 2+ as is the current standard.

Survival end points were disease free survival (DFS) and overall survival (OS). Overall survival was calculated from date of diagnosis to death from any cause. Disease free survival was calculated from date of diagnosis to any loco-regional recurrence or distant metastasis which ever occurred first. In the absence of any of the above mentioned events survival was censored at last follow up. Stage IV patients were also included in calculating overall survival for a true reflection of the study population

Statistical analysis

Data was analysed using SPSS version 19. The association between pregnancy and clinic-pathological parameters was analysed using chi square test. Survival curves were estimated using the Kaplan Meir method. Simple and Multiple Cox proportional hazard regression using matched pairs of the cohort as stratum (conditional) was used to calculate crude and adjusted hazard ratios with 95% confidence intervals for univariate and multivariable analysis of different prognostic factors. Any prognostic factor whose p-value at univariate level was less than 0.2 was considered eligible for multivariable analysis. P value < 0.05 was taken as significant.

RESULTS

Total 62 patients with pregnancy associated breast cancer were included in the study, for which we identified 124 controls [Table 1]. In PABC group, 42 cases were diagnosed during pregnancy while 20 were diagnosed within one year post-partum. The median (range) gestational age was 14 week (8-36 week). Eleven patients were identified having delay in diagnosis. [Median 6.36 months (Range 2-18 months)].

Table 1 summarizes the patient characteristics. A family history was present in 14.5% of PABC vs.7.3% in non PABC group. Mean age at first live birth was 23 years in PABC vs.22 years in non PABC. The median age at diagnosis was 31 years (Range: 23-41) & more than 40% of cases were stage III. In both groups around 30% of patients received neo-adjuvant chemotherapy. Around 48% received adjuvant & 10% received primary chemotherapy. The majority of patients received Anthracyclineb & Taxane based chemotherapy. All patients showing Her-2 neu over expression offered adjuvant Transtuzumab following delivery. However in PABC group 8 cases were showing over expression, out of which 2 received Trastuzumab because of financial constraints.

Mastectomy was done in more than 90 % of cases in PABC while it was performed in around 80% of cases in non PABC group. Adjuvant hormonal treatment was given to around 50 % in PABC vs. more than 60 % in non PABC group.

Pathological Characteristics: In PABC fifty six (90%) cases were invasive Ductal carcinoma & 2 (3.2 %) were invasive Lobular carcinoma.

Twenty four (39%) cases were grade III in PABC vs. twenty six (21%) in non PABC subset.(p=0.002) ER/PR status was positive in 45 %of cases in PABC vs. around 55 % in non PABC.(p=0.001) Her-2 neu over expression was seen in only eight (12.9%) cases in PABC. Triple negative subset was identified in 11 (17.7%) in PABC vs. sixteen (12.9%) in non PABC group [Table 2].(p=0.16)

Outcome: At a median follow up of 6 yrs. (range 1-20yrs); higher proportion of cases of patients relapsed (32.3% vs.12.1%) and died (25.8% vs. 11.3%) in PABC vs. Non-PABC [Table 3].(p=0.003 & 0.002 respectively).

Median overall survival in PABC group was 2.4 years (range: 4 months-8 years) compare with 5.5 years (range: 1.7 years-14 years.) in non PABC group. [Figure 1].(P=0.001).

The cases with PABC showed inferior DFS (median 1.5 years) as compared to non PABC (median 3.2 years). [Figure 2]. (p=0.01)

On univariate and multi variate analysis PABC, high grade and advanced stage was found to be an adverse prognostic factor [Table 4]. Triple negative breast cancer behaved in a same manner in PABC vs. Non PABC subset.

Pregnancy termination: In thirteen cases (21%) pregnancy was terminated, out of which 12 were terminated in 1st trimester & only one was done in 2nd trimester. Termination was done to avoid delay in starting treatment as in 1st trimester 5 cases were stage II & 5 were stage III at presentation.

DISCUSSION

A retrospective review of our data suggests that patients with PABC behave in an aggressive manner in comparison to non PABC cases, who were age and stage match controlled. Patients with PABC had a poorer prognosis (OS & DFS); they relapse earlier in spite of receiving standard treatments [Table 4].

Literature on the outcome of PABC is variable, some reports show a poor overall survival and disease free survival while others show similar outcome in both such groups.[8, 12-16] We opted to select controls matched for age and stage to ensure that comparisons were reasonable [Table 5].

We identified a lack of awareness in managing pregnancy associated lumps in the community leading to a delay in referral to specialist clinics while patient's fear of getting treatment in pregnancy presumed to affect foetal outcome prevented them from seeking specialist opinions leading to a delay in diagnosis reflecting a more advanced presentation.[8]

Data published from the M.D Anderson centre evaluating the impact of pregnancy on outcome of young patients (<35 years) showed no difference in overall survival, loco regional recurrence and distant metastasis.

Table 1: Demographics

Variables		PABC N (%)	Non PABC N (%)	P value
Total		62(100)	124(100)	
Age(years)	<35	43(69.4)	97(78.2)	
	35-39	17(27.4)	20(16.1)	Match
	≥40	02(3.2)	07(5.6)	
		Median (31.18)	Range (23-41)	
Stage(p)	0	02(3.2)	04(3.2)	
	1	08(12.9)	16(12.9)	
	2	20(32.3)	36(29.0)	Match
	3	26(41.9)	56(45.2)	
	4	06(9.7)	12(9.7)	
Neo adjuvant chemotherapy		19(30.6)	38(30.6)	Match
Adjuvant chemotherapy		30(48.4)	60(48.4)	Match
Primary chemotherapy		06(9.7)	12(9.7)	Match
Trastuzumab		02(3.2)	09(7.2)	
Surgery	BCT	02(3.2)	19 (15.3)	
	MASTECTOMY	58(93.6)	105 (84.7)	0.003*
	Not done	02(3.2)	00 (0)	
DXRT	Yes	34(54.8)	99(79.8)	
	No	28(45.2)	25(20.2)	0.000*
Adjuvant Hormonal	Yes	33(53.8)	78(62.9)	
	No	29(46.8)	46(37.1)	0.15
Type of Chemotherapeutic Rx				
Anthracycline(A) Based		11(36.6)	29(48.4)	
A+TAXANE Based		13(42)	20(32.4)	
CMF		06(20)	05(8.3)	

Match: ??; *p<0.05

Table 2: Pathologic Features of Patients

Total		PABC N (%) 62(100)	Non PABC N (%) 124(100)	P value
Histologic type	IDC	56(90.3)	118(95.2)	0.541
	ILC	02(3.2)	00(00)	
	Others	04(6.5)	06(4.8)	
Grade	I	01(1.6)	02(1.6)	0.002*
	II	37(59.7)	96(77.4)	
	III	24(38.7)	26(21.0)	
ER/PR	+	28(45.1)	68(54.8)	0.001*
	-	29(46.8)	46(37.1)	
	Not done	05(8.1)	10(8.1)	
Her-2/neu	+	08(12.9)	23(18.5)	---
	-	26(41.9)	42(33.8)	
	Not done	28(45.2)	59(47.7)	
Triple –ve	Yes	11(17.7)	16(12.9)	0.16
	No	51(82.3)	108(87.1)	

*p<0.05

Table 3: Outcome

Outcome		PABC N (%) 62(100)	Non PABC N (%) 124(100)	P value
Relapse	Local	00(00)	02 (1.6)	0.002
	Distant	20(32.3)	15(12.1)	
Survival status	No	42(67.7)	107(86.3)	0.000
	Alive	46(74.2)	110(88.7)	
	Expired	16(25.8)	14(11.3)	

Table 4: Univariate and Multivariate Analysis using Simple and multiple Cox Proportional Model for OS and DFS

	Univariate Analysis using Simple Cox Proportional Model for OS and DFS Hazard ratio (Confidence intervals)	
	Overall survival	**Disease-free survival**
Pregnant (yes versus no)	3.49 (1.67,7.32)	3.60 (1.88,6.91)
Stage (2 versus 3)	2.90 (1.27,6.59)	2.94 (1.39,6.24)
Grade (2 versus 3)	36.9 (11.1,122.0)	3.49 (1.82,6.67)
ER/PR (positive versus negative)	1.40 (0.64,3.05)	1.24 (0.63,2.43)
Chemotherapy (taxon based versus non taxon based)	0.72 (0.51,2.60)	1.20 (0.60,2.40)
1st born (early versus late)	0.63 (0.20,1.93)	0.97 (0.39,2.42)

	Multivariate Analysis using Multiple Cox Proportional Model for OS and DFS Hazard ratio (Confidence intervals)	
	Overall survival	**Disease-free survival**
OS, overall survival; DFS, disease-free survival.		
Pregnant (yes versus no)	3.68 (1.75,7.74)	4.09 (2.12,7.87)
Stage (2 versus 3)	3.09 (1.35,7.08)	3.40 (1.60,7.24)
Grade (2 versus 3)	40.76 (12.1,137.2)	3.33 (1.74,6.37)
ER/PR (positive versus negative)	0.86 (0.39,1.89)	1.12 (0.57,2.21)
Chemotherapy(taxon based versus non taxon based)	1.06 (0.47,2.38)	1.03 (0.51,2.08)
1st born (early versus late)	0.66 (0.21,2.05)	1.03 (0.41,2.56)

Table 5: Literature Review.

Author	Year	PABC	Non PABC	Outcome	P value
Halaska et al, 2009	1995-2007	32	32	No difference	0.449
Ali et al,2012	1990-2005	40	40	difference seen	0.01
Beadle et al 2009	1973-2006	104	483	No Difference	0.47
Azim et al 2012	1996-2010	65	130	No Difference	0.17
Moreira et al 2011	1980-2000	87	252	Difference seen	0.005
Rodriguez at al	1991-1999	779	4177	Difference seen	0.001
Aziz et al	7 years	24	315	No	>0.05
Our study	1987-2011	65	130	Poor outcome	0.001

The study was unmatched (104 PABC vs. 564 non PABC) taken only early breast cancer cases in contrary to our matched population included also advanced breast cancer (45%) for true reflection [8]

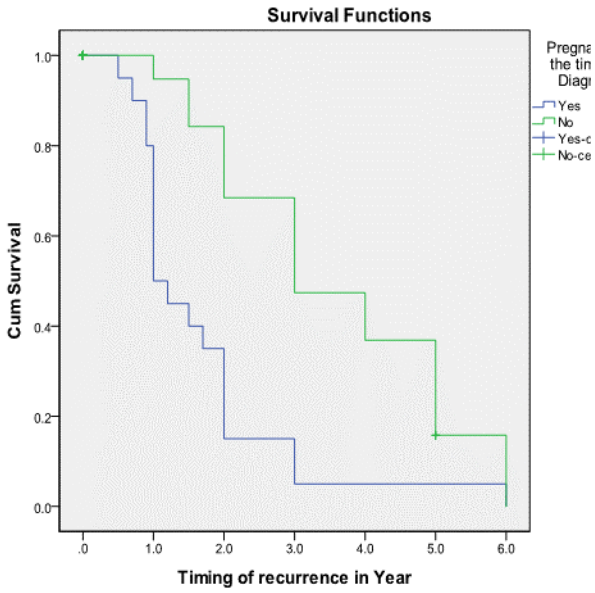

Figure 2: Disease free survival, PABC showed inferior DFS (median 1.5yrs) as compared to non PABC (median 3.2 yrs) p value (0.01).

One explanation for why PABC has a poor prognosis was given that diagnosis is delayed in new mothers[17-19] which are contrary to our observation where all 11 cases with delayed diagnosis were multiparous who came late for consultation having false immunity of not having breast cancer in multiparous.

Harvell at al published their data based on a genomic signature of PABC which showed a molecular distinction between PABC vs. non PABC suggesting mechanisms for PABC aggressiveness. Their analysis demonstrated that hormone mediated process related to cell cycle control in malignant epithelia and to immune response. ECM degradation and cell death in stream are enriched in PABC. Significant differences in genomic pathways important in PABC and its unique prognosis may lead to identification of unique targeted agents in future.[11]

Halaska et al study published a study in 2009 (32 PABC matched to 32 Non PABC) which showed no difference in overall survival between two groups which was attributed to a small sample size despite being age & stage matched [12]

Similar findings were observed in Amant et al data: In their cohort the multicentre registry was compiled pro- and retrospectively between 2003 and 2011 and it was compared with patients who did not have associated pregnancies, using an age limit of 45 years, they included 311 BCP and 865 non pregnant women. The results showed similar overall survival.[20] (p=0.51)

Aziz et al published a Case control study of novel prognostic markers and disease outcome in pregnancy/lactation-associated breast carcinoma and found that after a median follow-up of 72 months, there was no significant difference in the overall survival (OS) of test cases and controls as 54% deaths were recorded in test patients and 44% in controls at the end of this study ($p > 0.05$).They found that in spite of some significant differences in the expression of some prognostic markers, i.e. ER/PR, EGFR, PCNA , there was no significant difference in the OS of PABC vs. control group if compared stage for stage.[21]

Ali et al suggested that age greater than 30 years and an advanced stage in PABC group contributed to inferior survival .The other possible explanation they made for inferior survival was the immune suppressive state which exists in pregnancy with a high estrogen /progesterone levels.[13]

Azim et al reported that breast cancer arising at a younger age is associated with unique biology and poor prognosis. They reported that PABC had a significantly inferior disease free survival (52.1% vs.74.3% p=0.01) but overall survival was similar (p=0.17) adjusted for age and stage.[10,22]

Dimitrakakis et al postulated that poor outcome in PABC group is due to most of their cases diagnosed in third trimester when there is high hormonal milieu

which is contrary to our observation where the mean trimester was 14 week.[23]

Madaras et al showed that PABC patients with a Luminal B profile and Triple negative tumours had inferior outcomes but in our study triple negative disease has no influence on the outcome.[24]

Another group observed poorer survival possibly due to the presence of adverse prognostic features such as lymph node metastases, negative hormone receptors, and tumour grade III, as well as a delay in diagnosis with a higher rate of advanced stages.[25]

We hypothesize that pregnancy itself has an independent effect on prognosis by influencing the biology of breast cancer. The continuous high hormone levels of pregnancy may play a role in tumour aggressiveness and an advanced stage at presentation. Recently, it has been shown that pregnancy led to a transient 11-fold increase in mammary stem cell MaSC numbers, probably mediated through paracrine signalling from RANK ligand. The augmented MaSC pool indicates a cellular basis for the short-term increase in breast cancer incidence that accompanies pregnancy.[26] In humans, a recent in silico analysis has shown that both MaSc and RANK ligand are highly expressed and highly correlated in breast cancer arising at younger age <40 years. [27]

Recent work by Azim et al showed that two pathways are enriched in tumors diagnosed during pregnancy: the G protein-coupled receptor pathway and the serotonin receptor pathway (FDR <0.0001).[22] Tumours diagnosed during pregnancy had higher expression of PD1 (PDCD1; P=0.015), PDL1 (CD274; P=0.014), and gene sets related to SRC (P=0.004), IGF1 (P=0.032), and β-catenin (P=0.019). Their expression increased almost linearly throughout gestation when evaluated on the normal breast using a pregnant mouse model underscoring the potential effect of the breast microenvironment on tumour phenotype. Diagnosis during pregnancy impacts the breast cancer transcriptome including potential cancer targets.[28]

Our study design has limitations. Data were retrospectively pooled; the sample size is small and was a single centre study. However, it was chosen to create a more homogeneous control group, with few missing data, Histological data were centrally confirmed, with complete information on family history of breast cancer.

CONCLUSION

In general Women with PABC have a worse long term outcome compared with the non PABC counter parts. It is uncertain whether this could be attributed to different tumour biology or delayed presentation. An increased awareness among clinicians may help reduce the undue delays in diagnosis and treatment. Evolving concepts in cancer biology and available data enforces need for more research prospective randomized clinical trials to validate the findings.

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