

## Amenorrhea Induced By Chemotherapy In Premenopausal Breast Cancer Patients (Retrospective Study)

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### Abstract

**Background:** Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. The American Cancer Society estimates that 249, 260 Americans will be diagnosed with invasive breast cancer.

**Objectives:** This is a retrospective study aiming to identify the frequency of amenorrhea (ovarian failure) after different chemotherapy regimens in premenopausal patients with breast cancer as well as the associated other risk factors that could influence the rate of amenorrhea.

**Patients and Methods:** This study will include patients with breast cancer with at least a minimum follow up of six months after last cycle of chemotherapy either clinically or by E2 and FSH. Expected number of enrolled patients in this study is around 100 patients.

**Results:** Patients who had HER 2 negative IHC stain had significantly lower rates of Chemotherapy Induced Amenorrhea (CIA) when compared to those HER 2 positives with p value 0.001. In our study we have found a correlation between DFS and CIA which imply that patients who had CIA had better survival than those with CIA however this difference was not significant, p value 0.129, Overall survival show no difference based on CIA p value 0.319.

**Conclusion:** CIA is a main concern for females treated with breast cancer, it was found correlated to age, tumor stage, tumor biology and type of surgery. More prospective studies are needed to confirm correlation between CIA and prognosis of breast cancer, nonetheless other treatment regimens and malignancies should be investigated.

**Keywords:** Chemotherapy; Amenorrhea; Premenopausal Breast Cancer Patients.

### INTRODUCTION

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. The American Cancer Society estimates that 249, 260 Americans will be diagnosed with invasive breast cancer and 40, 890 will die of the disease in the United States in 2016.<sup>1</sup>

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, ALN status, tumor hormone receptor (ER & PR) content, tumor HER2 status. Adjuvant endocrine therapy is an integral component of care for endocrine-dependent breast cancer (EDBC). The goal of this type of therapy is to counteract the production and the action of oestrogens.<sup>2</sup>

The ovaries of premenopausal women who received chemotherapy typically have normal to mildly decreased numbers of primordial follicles and a greater decrease in the numbers of maturing follicles,

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indicating a greater effect on follicular development than on oocytes. Consistent with these histologic findings are the clinical observations that many women are amenorrhoeic during chemotherapy, often with high serum gonadotrophin concentrations, but that menstrual function and fertility often return several months to years after the cessation of therapy.<sup>3</sup>

Chemotherapy-induced amenorrhea is a well-recognized side effect of cytotoxic chemotherapy. These drugs appear to have a greater effect on follicular development than on oocytes, with variable degrees of subsequent ovarian dysfunction. Some women develop complete follicular depletion and permanent ovarian failure during chemotherapy, while others may become amenorrhoeic during therapy, but then have subsequent return of ovarian function, menstrual cycles, and fertility, months to years after the cessation of therapy. There are well-recognized risk factors for chemotherapy-induced

amenorrhea or ovarian failure, such as age, chemotherapy regimen, subsequent use of endocrine therapy and genetics.<sup>4</sup>

### PATIENT AND METHODS

This retrospective study included all patients with breast cancer with at least a minimum follow up of six months after last cycle of chemotherapy either clinically or by E<sub>2</sub> and FSH. Number of patients enrolled in this study is 97 patients from January 2009 to December 2015.

**Inclusion criteria:** Female patient, Age > 18 years, pathologically confirmed breast cancer, Premenopausal at the diagnosis of breast cancer, Breast cancer at any stage and Six month or more follow up after last cycle of chemotherapy.

**Exclusion criteria:** Postmenopausal women, Patient with double malignancy, Hysterectomy and Any kind of oophorectomy.

**The following data collected from patients' files:** Personal data (age, sex, marital state, sibling), Menstrual history (menarche, regularity), comorbidities (diabetes, hypertension, thyroid dysfunction), contraceptive history, disease criteria (date of first diagnosis, extent of disease, histological type, stage), treatment related data (chemotherapy regimen, number of cycles, regularity), amenorrhea related data (time of amenorrhea, reversibility).

#### ETHICAL APPROVAL:

Informed consents were obtained from all participants during their follow up at clinic, and data confidentiality was maintained throughout the study and any resulting publication anonymously.

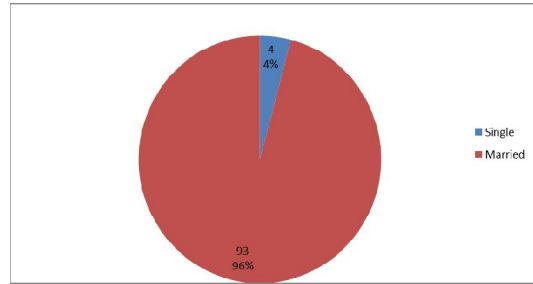
#### STATISTICAL METHODS:

Amenorrhea defined as absence of menstruation in a woman of reproductive age for more than 6 months either clinically or by E<sub>2</sub> <20, FSH >20. Data presented as mean and standard deviation or median and range as appropriate. Categorical data will be presented as frequency and percentage. Relation between categorical data done using or appropriate statistical test. For quantitative data comparison between two groups done using either parametric or non parametric t- test. P-value less than 0.05 will be considered significant.

### RESULTS

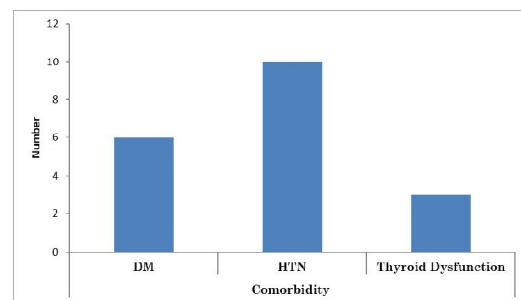
#### Patient's characteristics:

The mean age of all patients was 41.3 years ranges between (28-54) years. Out of these patients, 93 (95.9%) were married while 4 patients (4.1%) were single. Seventy-seven patients (79.4%) gave history of regular menses while 16 (21.6%) patients had history for irregular menstruation. Table (1), Figure (1)



**Fig. 1:** Pie diagram shows marital status of patients included in the current study.

Diabetes was observed in 6 patients (6.2%) and 10 patients were hypertensive (10.3%), while 3 patients (3.1%) were diagnosed with thyroid disorders. Table (1), Figure (2)



**Fig. 2:** Histogram shows comorbidities of patients included in the current study.

#### Histopathological characteristics:

Invasive duct carcinoma diagnosed in 93 patients (95.8%), invasive lobular carcinoma also diagnosed in 2 patients (2.1%), while 2 patients (2.1%) diagnosed with mucinous variant. Table (2), Figure (3)

MRM done for 55 patients (56.7%) while conservative breast surgery done for the rest of the patients (43.3%). Figure (4)

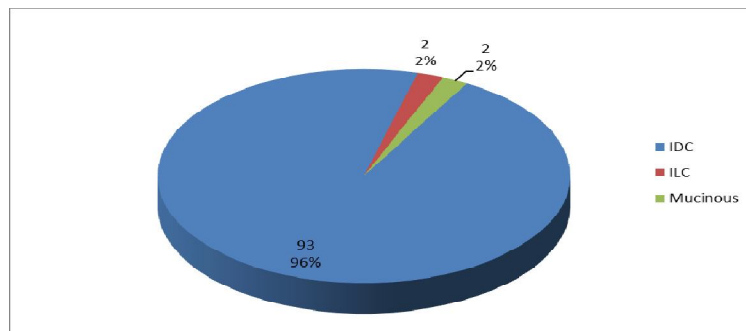
Eight patients (8.2%) presented with T1 staging, T2 staging found in 60 patients (61.9%), and 19 patients (19.6%) had T3 staging, while 10 patients (10.3%) had T4B disease. Table (2)

Positive estrogen receptors found in 82 patients (84.5%). while rest of patients (15.5%) were negative. Positive progesterone receptor found in 77 patients (79.4%), while rest of patients (20.6%) were negative. Her2neu status was over expressed in 21 patients (21.6%). While 77 patients (78.4%) were negative. Table (2), Figure (5)

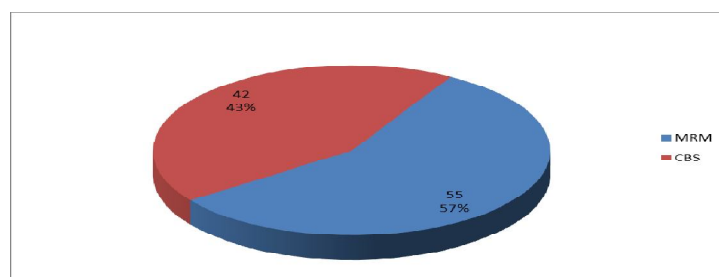
		Number	%
Age (years)	Mean ±SD	41.3±5.7	
	Range	28-54	
Marital Status	Single	4	4.1
	Married	93	95.9
Menarche age	Mean ±SD	12.7±1.0	
	Range	11-14	
Menstrual Regularity	Yes	77	79.4
	No	16	21.6
Siblings	Median (Range)	3(0-6)	
Contraception*	Hormonal	41	42.3
	IUD	52	53.6
Comorbidity	DM	6	6.2
	HTN	10	10.3
	Thyroid Dysfunction	3	3.1
Family History	No	82	84.5
	Yes	15	15.5

\*among married

**Table 1:** Patient characteristics



**Fig. 3:** Pie diagram shows histopathological characteristics of tumors included in the current study.



**Fig. 4:** Pie diagram shows type of surgery done for patients included in the current study.

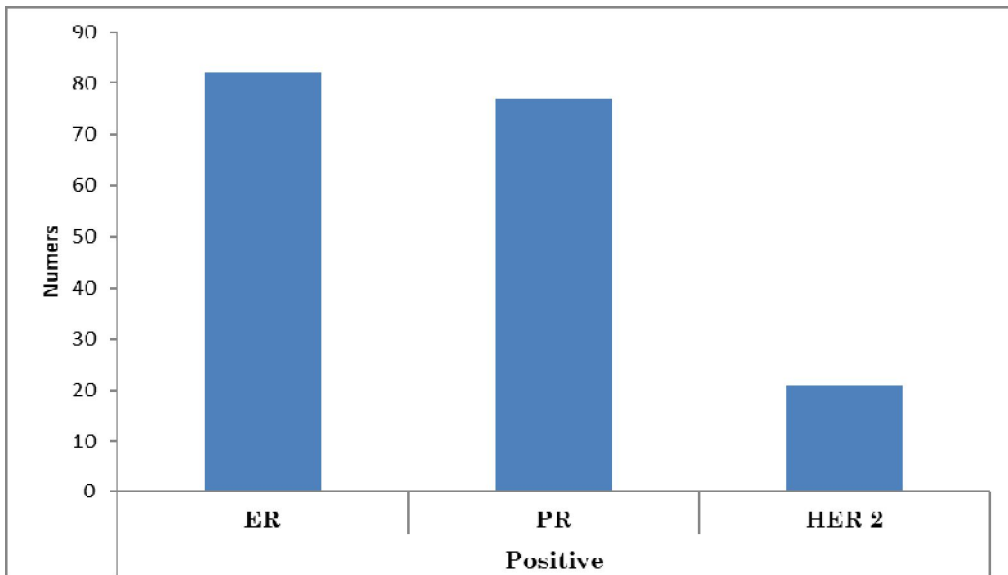


Fig. 5: Histogram shows immunophenotyping pattern of study populations.

		Number	%
Surgery	MRM	55	56.7
	CBS	42	43.3
T Stage	T1	8	8.2
	T2	60	61.9
	T3	19	19.6
	T4B	10	10.3
N Stage	N0	30	30.9
	N1	33	34.0
	N2	27	27.8
	N3	7	7.2
Histology	IDC	93	95.8
	ILC	2	2.1
	Mucinous	2	2.1
Grade	II	95	97.9
	III	2	2.1
ER	Negative	15	15.5
	Positive	82	84.5
PR	Negative	20	20.6
	Positive	77	79.4
HER 2	Negative	76	78.4
	Positive	21	21.6

Table 2: Histopathological characteristics

	Induced Amenorrhea										P value
	No					Yes					
	Median	Min.	Max.	Q1	Q3	Median	Min.	Max.	Q1	Q3	
LN Resected	17	8	30	14	20	18	12	22	15	21	0.669
LN Positive	2	0	20	0	5	3	0	10	2	6	0.030
Cycles #	6	4	8	4	8	6	3	8	6	8	0.411
E2 Level	111.5	15	1680	45	230	14	5	19	10	19	<0.001
FSH Level	16	5	61	11	20	53	25	123	36	85	<0.001

Table 3: Induced amenorrhea



Induced Amenorrhea		N	Mean	SD	P value
Age	No	56	38.9	4.7	<0.001
	Yes	32	45.0	4.3	
Menarche	No	56	12.5	0.9	0.064
	Yes	32	12.8	0.7	
Largest Size	No	55	4.3	1.5	0.259
	Yes	26	4.8	2.0	

SD: standard deviation,  $p \leq 0.05$  is considered statistically significant, analysis done by independent t test

**Table 4:** Age of menarche

		Induced Amenorrhea				p value
		No		Yes		
		Count	%	Count	%	
Marital Status	Single	4	100.0	0	0.0	0.122
	Married	52	61.9	32	38.1	
Regularity	No	6	30.0	14	70.0	<0.001
	Yes	50	73.5	18	26.5	
Contraception	Hormonal	29	70.7	12	29.3	0.035
	IUD	19	48.7	20	51.3	
	Others-None	4	100.0	0	0.0	
DM	No	55	67.1	27	32.9	0.013
	Yes	1	16.7	5	83.3	
HTN	No	52	66.7	26	33.3	0.099
	Yes	4	40.0	6	60.0	
Thyroid Dysfunction	No	53	62.4	32	37.6	0.183
	Yes	3	100.0	0	0.0	
Family History	No	50	65.8	26	34.2	0.291
	Yes	6	50.0	6	50.0	
Surgery	MRM	23	46.9	26	53.1	<0.001
	CBS	33	84.6	6	15.4	
Histology	IDC	52	61.9	32	38.1	0.302
	ILC	2	100.0	0	0.0	
	Mucinous	2	100.0	0	0.0	
Grade	II	54	62.8	32	37.2	0.532
	III	2	100.0	0	0.0	
ER	Negative	3	50.0	3	50.0	0.472
	Positive	53	64.6	29	35.4	
PR	Negative	8	72.7	3	27.3	0.503
	Positive	48	62.3	29	37.7	
HER 2	Negative	51	72.9	19	27.1	<0.001
	Positive	5	27.8	13	72.2	
T Stage	T1	6	75.0	2	25.0	0.003
	T2	38	70.4	16	29.6	
	T3	11	68.8	5	31.3	
	T4B	1	10.0	9	90.0	
N Stage	N0	19	79.2	5	20.8	0.217
	N1	21	63.6	12	36.4	
	N2	14	51.9	13	48.1	
	N3	2	50.0	2	50.0	

$p \leq 0.05$  is considered statistically significant, analysis done by Chi square test t stage t4B is statistically significant from other stages.

**Table 5:** Factors in relation with amenorrhea status.

Factors	n	DFS %			Median(months)	p value
		2 years	3 years	5 years	(95% CI)	
All	97	96.9	90.6	85.0	82.3	NA
<b>Age</b>						
≤40	48	95.8	93.2	84.7	82.3	0.879
>40	49	97.9	88.1	80.7	NA	
<b>Marital Status</b>						
Single	4	100	100	100	NA	0.467
Married	93	96.8	90.3	84.4	NA	
<b>Siblings</b>						
≤3	60	96.6	90.7	87.5	82.4	0.933
>3	33	97.0	89.4	78.8	NA	
<b>Menarche Age</b>						
<13	34	100	100	94.4	NA	<b>0.023</b>
≥13	63	95.2	86.0	80.4	82.3(65.4-99.3)	
<b>Regular Cycles</b>						
No	20	100	93.8	82.0	NA	0.604
Yes	77	96.0	89.9	85.3	82.4(82.0-82.9)	
<b>Contraception</b>						
Hormonal	41	100	100	94.7	NA	0.009
IUD	48	93.7	85.0	73.2	82.3	
Others-none	4	100	100	100	NA	
<b>DM</b>						
No	91	96.7	91.6	85.6	82.3	0.520
Yes	6	100	75.0	NA	NA	
<b>HTN</b>						
No	87	96.5	89.7	83.7	NA	0.194
Yes	10	100	100	100	NA	
<b>+ve Family history</b>						
No	82	97.6	90.2	85.8	82.4	0.885
Yes	15	92.9	92.9	79.6	NA	
<b>Surgery</b>						
MRM	55	94.5	83.8	77.4	82.3(40.8-123.9)	0.054
CBS	42	100	100	95.5	NA	
<b>Stage</b>						
Early	68	98.5	98.3	92.7	NA	<b>0.001</b>
Late	29	93.1	73.5	67.9	82.3	
<b>Size</b>						
<4.5	41	97.1	97.1	92.6	82.3(52.9-111.7)	0.684
≥4.5	49	98.0	91.2	84.0	88.6	

P≤0.05 is statistically significant, CI: confidence interval, NA: not applicable

**Table 6:** Disease free survival among all patients' groups

### DISCUSSION

Breast cancer is the commonest malignancy affecting females worldwide, it is estimated to be the fifth cause of death in cancer related mortalities. Breast cancer is a systemic disease, meaning that it require systemic treatment as main line of therapy, chemotherapy is the key player in adjuvant treatment of breast cancer patients, may regimens has been discussed in literature proving that Anthracycline based chemotherapy lead to best prognosis, in addition to paclitaxel it has improved the OS and DFS in patients with advanced stages.<sup>5</sup>

Chemotherapy induced amenorrhea and fertility preservation has been a critical point of discussion

since<sup>6,7</sup> found that 41% of breast cancer survivors experienced amenorrhea during treatment, while Melanie and colleagues confirmed that 31% of their sample had amenorrhea during chemotherapy treatment, in our study 33% had chemotherapy induced amenorrhea.

In the current study, age was found to be statistically correlated to chemotherapy induced amenorrhea as patients with older ages are more borne for permanent amenorrhea and ovarian failure while younger ages were more borne to transient amenorrhea with p value 0.0001, any authors have confirmed same results.<sup>8,9</sup>

It is believed that regularity of menses is correlated with induction of amenorrhea post chemotherapy as detailed by <sup>10</sup> patients who had a Hodgkin's disease with irregular menses experienced longer amenorrhea period than those with regular one, in our study patients with regular menses had lower incidence of chemotherapy induced amenorrhea with p value 0.001 when compared to those with irregular menses.<sup>10</sup>

Our study was the first to find a statistically significant correlation between chronic disease as DM and CIA with p value 0.013 when compared to patients who didn't suffer from DM, nonetheless we discovered that patients who had CBS had lower rates of CIA, this may be due to younger women tend to have conservative surgeries to maintain the cosmetic contour of the breast while older women usually go for MRM to avoid adjuvant chemotherapy and postoperative radiation p value 0.001.

Knowing that in our sample patients who had HER 2 negative IHC stain had significantly lower rates of CIA when compared to those HER 2 positive stain with p value 0.001. In the current study, we have found a correlation between DFS and CIA which imply that patients who had CIA had better survival than those with CIA however this difference was not significant, p value 0.129, Overall survival show no difference based on CIA p value 0.319.

Many limitations have been faced in our study, being a retrospective study, it had missed data and incomplete follow up records, larger prospective studies are needed to confirm prognosis of CIA on patient's survival, as well as investigation of other protocols and malignancies.

### CONCLUSION

CIA is a main concern for females treated with breast cancer, it was found correlated to age, tumor stage, tumor biology and type of surgery. More prospective studies are needed to confirm correlation between CIA and prognosis of breast cancer, nonetheless other treatment regimens and malignancies should be investigated.

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