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Comparative study between effect of both drugs Tamoxifen versus Letrozole on endometrial thickness as Hormonal adjuvant therapy in breastcancer

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Abstract---Background: Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer related deathin women. About eighty percent of breast cancers express Estrogen receptors. Long term survival of hormone receptor positive breast cancer patients was significantly improved after introduction of adjuvant hormonal therapy. Different classes of hormonal agents with different mechanisms of action and side effects are available. Tamoxifen has known proliferative effect on endometrium. This may lead to

hyperplasia, bleeding and endometrial cancer. Objective: to compare between effects of tamoxifen versus effect of letrozole on the endometrial thickness as adjuvant Endocrine treatment inhormone receptor positive breast cancer. Patients and methods: 66 patients were enrolled in the study from May 2021 to November 2021; they were randomized to receive either tamoxifen or letrozole. Endometrial thickness was measured at baseline, after three and six months from start of treatment. Results: No significant difference in endometrial thickness in the two groups.

Keywords---breast cancer, hormonal receptor positive breast cancer, endometrial thickness, tamoxifen, letrozole.

Introduction

Breast cancer is the most common cancer in women across the globe. Breast cancer is the fifth leading cause of cancer related death and the first most common cause of cancer death in females (Lei S. et al., 2021).Breast cancer incidence in Egypt is 52.4/100 000 (Sharma R., 2021). Number of new cases diagnosed per year is more than 22,000 cases (Abdelaziz A. et al., 2020).Breast cancer is subdivided into several subtypes which differ in biology and treatment algorithm. Hormone receptor positive breast cancer represents about 80% of breast cancer cases (Lumachi F. et al., 2015).The use of Tamoxifen as adjuvant endocrine therapy for Hormone receptor positive breast cancer has led to 31% reduction in breast cancer mortality (Verma S. et al., 2009). Tamoxifen is the oldest and most-prescribed selective estrogen receptor modulator (SERM). Tamoxifen acts by competitive inhibition of Estrogen receptors in breast cancer cells and inhibits their proliferation (McDonnell DP and Wardell SE., 2010). Tamoxifen has agonistic effect on various tissues as uterus, bone and liver (Silva LAS. et al., 2017). Its effect on endometrial cells leads to development of endometrial hyperplasia, polyps, growth of uterine fibroids, malignant transformation to endometrial carcinomas and uterine sarcomas (Jindal A. et al., 2015).

In premenopausal women there is no increased risk of endometrial carcinoma with the use of Tamoxifen (Cheng W-F. et al., 1997).Postmenopausal women receiving Tamoxifen are at increased risk of developing endometrial carcinoma (Saccardi C. et al.,2022).Women taking tamoxifen should be informed about the potential risks of Tamoxifen use on the endometrium and any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated. Routine endometrial surveillance has not proved to be effective in increasing the early detection of endometrial cancer in women using tamoxifen and is not recommended (Fleming CA. et al., 2018).Aromatase inhibitors inhibit peripheral estrogen synthesis which occurs in adipose tissues, muscles and breasts. They inhibit the action of aromatase enzyme which converts androgens to estrogens (Miller WR., 2003). Compared to Tamoxifen Aromatase inhibitors reduce breast cancer recurrence by 30% (Group EBCTC., 2015).

Patients and Methods

This study was carried out as a randomized control study which done at Dar El-salam cancercenter Medical Oncology department for about 6 months.

Patients

Female patients diagnosed with hormonal receptor positive breast cancer and are candidates for adjuvant endocrine therapy.

The studied participants were divided into two groups

- **Group1:** were randomized to receive adjuvant Tamoxifen 20mg daily for 5 years
- **Group 2:** were randomized to receive adjuvant Letrozole 2.5mg daily for 5 years.

Inclusion criteria

Postmenopausal women requiring adjuvant endocrine therapy for hormonal receptor positive breast cancer.

Exclusion criteria

Women with previously undiagnosed vaginal bleeding, women with history of hysterectomy, women with previously diagnosed gynecological cancers, women with history of receiving hormonal replacement therapy and women using anticoagulants for any cause.

Sample size estimation

The required sample size was calculated depending on one of theprimary outcomes that is vaginal bleeding and increased endometria Thickness with the two hormonal agents. Previous study has shown that 3.3% of letrozole users have vaginal bleeding compared to 6.6% of the tamoxifen users (Collaborative study Group on Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials, 2015), and with power of the study of 80% and alpha value of 0.05(Dobson, 1984), and adding 10% as expected dropout, sample size of 33 women per group was be required (total sample size=66women)

Randomization

Enrolled women were allocated to one of two treatment arms (tamoxifen and letrozole) using simple randomization. Randomization of the patients was achieved by using 66 sealed envelopes method, 33 envelopes carried the label Tamoxifen group, and the other 33 carried the label Letrozole group and everywoman fulfilling the inclusion criteria, and had nothing of the exclusion criteria waslet to choose one card blindly then according to the card she has chosenwas added to one of the two groups.

Methods of the study

An informed written consent was obtained from all participants after enrollment in the study.

All of the studied women in both groups were subjected to the following

Complete history taking including: Personal history (name, age, residence, job), menstrual history (age at menarche, menopause, history of menstrual irregularities), complete obstetric history, past history of gynecological abnormalities and history of any drug intake especially those which increase possibility of bleeding. General examination stressing on assessment of blood pressure and anysigns of hematological disorders like skin patches or ecchymosis. Baseline laboratory tests: complete blood picture and coagulationprofile (PT, PTT, INR, and Clotting time).

Studied drugs

Women in group 1 (Tamoxifen group) received Tamoxifen 10mg daily.
Women in group 2 (Letrozole group) received Letrozole 2.5 mg daily.

Outcome measures

Participants were assessed for presence of vaginal bleeding at the start and after three and six months of initiation of treatment by: Clinically examination, radiologically using transvaginal ultrasound and Laboratory evaluation bycomplete blood picture.

Outcome measures were

Abnormal vaginal bleeding, Increased endometrial thickness and Decreased Hemoglobin level.

Results

Table 1
Comparison according to demographic characteristics andmedical, surgical& family history

Variables	Measures	Tamoxifen (N=33)	Letrozole(N=33)	p-value
Age (years)	Mean±SD	54.2±10.1	55.2±10.9	^0.682
	Range	40.0–81.0	39.0–79.0	
Age at menarche(years)	Mean±SD	13.4±1.0	13.5±0.9	
	Range	11.0–15.0	12.0–16.0	^0.896
Medicalhistory	Free	15 (45.5%)	17 (51.5%)	#0.622
	Hypertension	12 (36.4%)	9 (27.3%)	#0.428
	Diabetesmellitus	7 (21.2%)	7 (21.2%)	#0.999
	Cholecystitis	3 (9.1%)	2 (6.1%)	§0.999
	Bronchialasthma	1 (3.0%)	2 (6.1%)	§0.999

Surgicalhistory	Free	21 (63.6%)	20 (60.6%)	#0.800
	Cesareansection	4 (12.1%)	6 (18.2%)	#0.492
	Tonsillectomy	2 (6.1%)	2 (6.1%)	§0.999
	Appendectomy	3 (9.1%)	3 (9.1%)	§0.999
	Mass removal	3 (9.1%)	2 (6.1%)	§0.999
	Dilatation& curettage	1 (3.0%)	1 (3.0%)	§0.999
Family history of malignancy		4 (12.1%)	5 (15.2%)	§0.999

^Independent t-test. #Chi square test. §Fisher's Exact test. *Significant Table (1) shows that: No significant difference between Tamoxifen and Letrozole groups regarding age, age at menarche and medical, surgical&family history.

Table 2
Comparison according to endometrial thickness

Time	Tamoxifen(N=33)	Letrozole(N=33)	§ p-value
Month-3	4 (12.1%)	2 (6.1%)	0.672
Month-6	6 (18.2%)	3 (9.1%)	0.475

#Chi square test. §Fisher's Exact test

Table (2) and figure (1) show that: Endometrial thickness at differentfollow up times was non-significantly more frequent in Tamoxifen group than in Letrozole group.

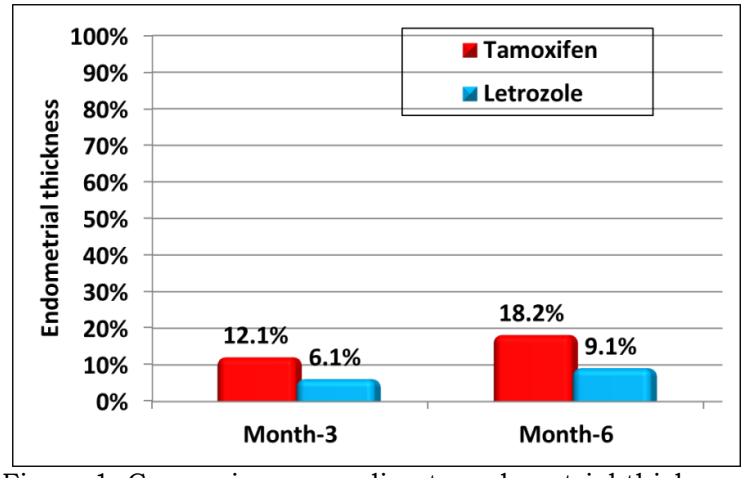

Figure 1. Comparison according to endometrial thickness

Table 3
Comparison according to vaginal bleeding

Time	Tamoxifen(N=33)	Letrozole(N=33)	§ p-value
Month-3	4 (12.1%)	2 (6.1%)	0.672
Month-6	5 (15.2%)	3 (9.1%)	0.708

§Fisher's Exact test

Table (3) and figure (2) show that: Vaginal bleeding at different followup times was non-significantly more frequent in Tamoxifen group than in Letrozole group.

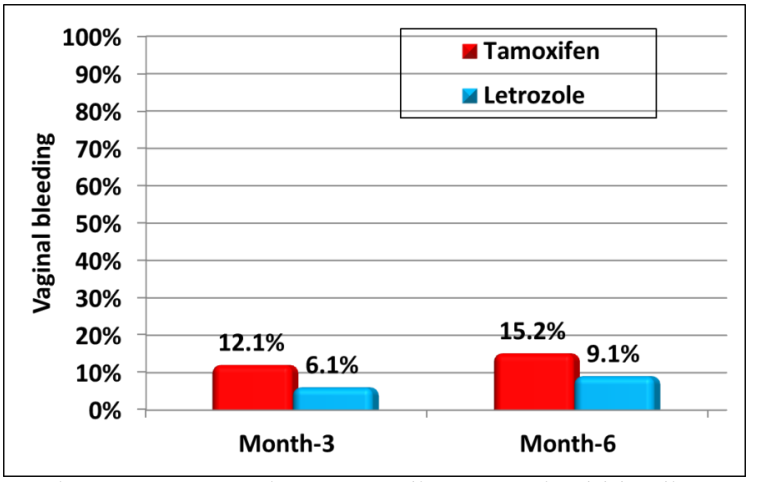

Figure 2. Comparison according to vaginal bleeding

Table 4
Comparison according to hemoglobin (gm. /dL)

Time	Measures	Tamoxifen (N=33)	Letrozole(N=33)	^p- value
Baseline	Mean±SD	11.8±0.9	11.7±1.1	0.642
	Range	10.5–13.6	10.1–13.4	
Month-3	Mean±SD	11.4±0.8	11.6±1.1	0.399
	Range	9.6–12.9	10.0–13.3	
Month-6	Mean±SD	11.0±1.0	11.5±1.1	0.045*
	Range	8.7–12.8	10.1–13.3	
Change at month-3	Mean±SD	-0.4±0.6	-0.1±0.1	0.002*
	Range	-1.9–0.0	-0.4–0.0	
	#p-value	<0.001*	<0.001*	
Change at month-6	Mean±SD	-0.8±1.1	-0.2±0.3	0.002*
	Range	-3.6–0.0	-0.9–0.0	
	#p-value	<0.001*	0.002*	

Change=Month-baseline. ^Independent t-test. #paired t-test. *Significant Table (4) and figure (3) show that: No significant difference between

Tamoxifen and Letrozole groups regarding baseline hemoglobin. Hemoglobin in months 3 and 6 were lower in Tamoxifen group than in Letrozole group, but the differences were statistically significant only in month-6. Hemoglobin reductions in months 3 and 6 were significantly higher in Tamoxifen group than in Letrozole group.

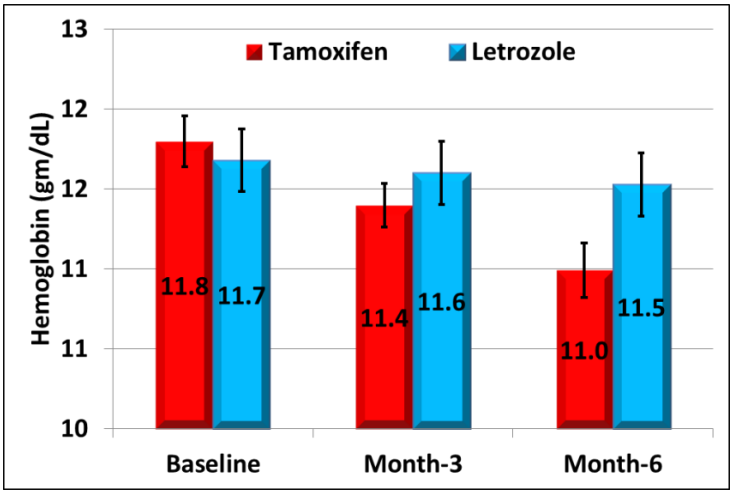

Figure 3. Comparison according to hemoglobin level

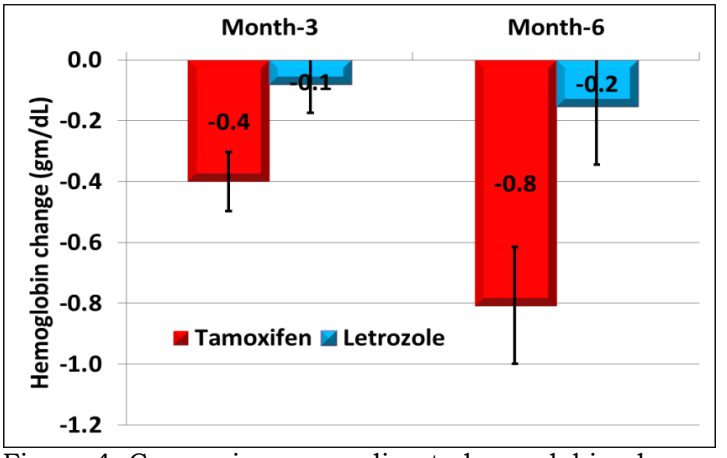

Figure 4. Comparison according to hemoglobin change

Table 5
Comparison according to need to hemostatic drugs

Time	Tamoxifen (N=33)	Letrozole (N=33)	§ p-value
Monnth-3	2 (6.1%)	0 (0.0%)	0.492
Month-6	5 (15.2%)	2 (6.1%)	0.427

§Fisher's Exact test

Table (5) and figures (5) show that: Hemostatic drugs were non- significantly needed more frequent in Tamoxifen group than in Letrozole group at months 3 and 6.

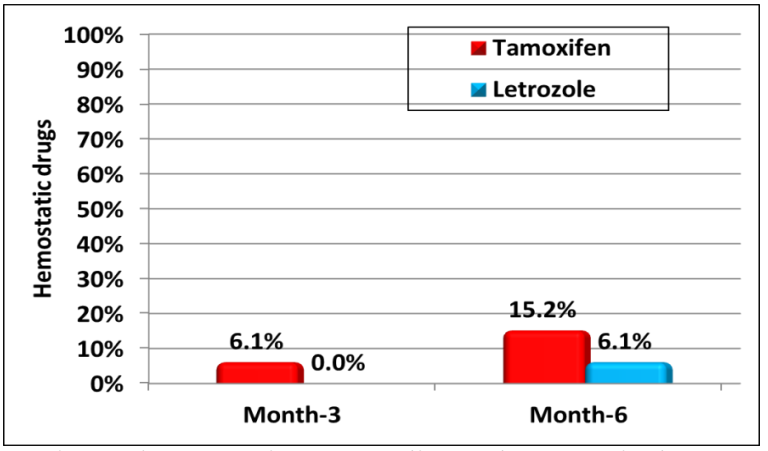

Figure 5. Comparison according to hemostatic drugs

Table 6
Comparison according to need to iron tablets

Time	Tamoxifen(N=33)	Letrozole(N=33)	p-value
Monnth-3	5 (15.2%)	3 (9.1%)	§0.708
Month-6	8 (24.2%)	4 (12.1%)	#0.202

#Chi square test. §Fisher's Exact test

Table (6) and figures (6) show that: Iron tablets were non-significantlyneeded more frequent in Tamoxifen group than in Letrozole group at months3 and 6.

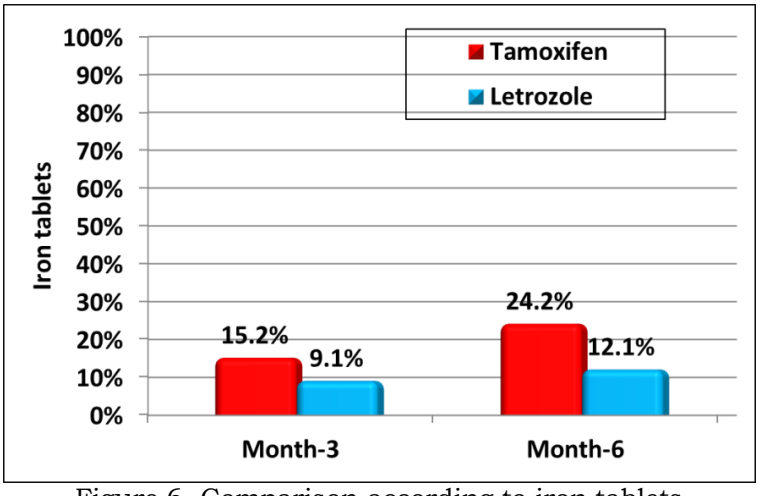

Figure 6. Comparison according to iron tablets

Table 7
Comparison according to dilatation and curettage

Variables	Tamoxifen(N=33)	Letrozole(N=33)	§ p-value
Dilatation and curettage	4 (12.1%)	2 (6.1%)	0.672

Time	Month-3	0 (0.0%)	0 (0.0%)	Not applicable
	Month-6	4 (100.0%)	2 (100.0%)	
Findings	Malignant	1 (25.0%)	0 (0.0%)	0.999
	Benign	3 (75.0%)	2 (100.0%)	

§Fisher's Exact test

Table (7) and figures (7) show that: Dilatation and curettage was non-significantly more frequent in Tamoxifen group than in Letrozole group. All cases were at month-6 in both groups. Malignancy non-significantly found only in Tamoxifen group

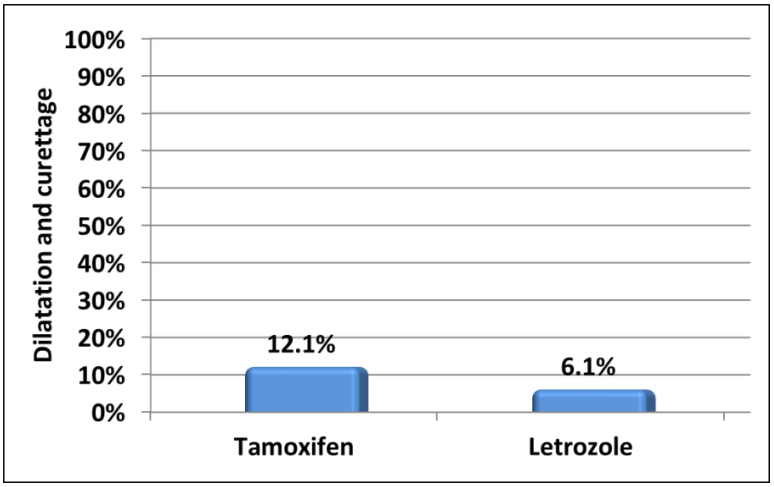

Figure 7. Comparison according to dilatation and curettage

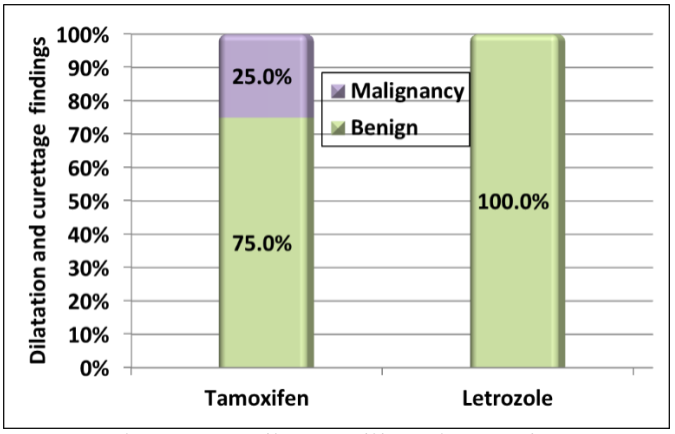

Figure 8. Comparison according to dilatation and curettage findings

Table 8
Comparison according to hysterectomy

Variables		Tamoxifen(N=33)	Letrozole(N=33)	§ p-value
Hysterectomy		2 (6.1%)	0 (0.0%)	0.492
Time	Month-3	0 (0.0%)		
	Month-6	2 (100.0%)		

§Fisher's Exact test

Table (8) and figures (9) show that: Hysterectomy was non- significantly occurred only in Tamoxifen group. All of them needed at month-6.

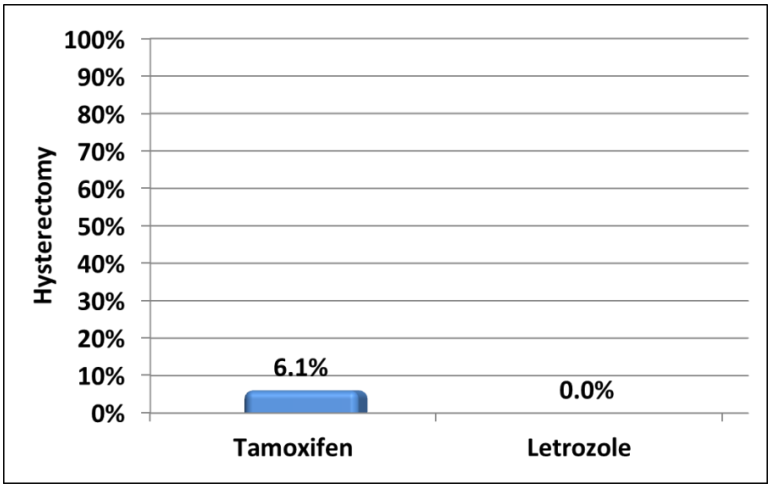

Figure 9. Comparison according to hysterectomy

Table 9
Comparison according to mortality

Variables	Tamoxifen(N=33)	Letrozole(N=33)	§ p-value
Mortality	0 (0.0%)	0 (0.0%)	Not applicable
Survival	33 (100.0%)	33 (100.0%)	

§Fisher's Exact test.
Table (9) show that: Mortality was not recorded in either group.

Discussion

The present study aimed to compare the effect of both Tamoxifen and Letrozole as adjuvant therapy in hormonal receptor positive breast cancer regarding abnormal vaginal bleeding, increased endometrial thickness and decreased hemoglobin level. The study was carried out as a group- comparative study on a total of 66 postmenopausal women with hormonal receptor positive breast cancer indicated for adjuvant endocrine therapy.Enrolled women were allocated to one of the treatment arms (Tamoxifen and Letrozole) using simple randomization by choosing one of 66 sealed envelopes, 33 envelopes carry the label Tamoxifen group and the other 33 carry the label Letrozole group and every woman fulfilling the inclusion criteria and has nothing of the exclusion criteria. The collected data is given to the assistant nurse and at the end of follow up visits after 6 months, the datawas analyzed.

The present study showed that there was no statistically significant difference between tamoxifen and letrozole groups regarding abnormal uterine bleeding either after 3 and 6 months of treatment. These results were inconsistent with the study done by Henning Mouridsen et al.,2003. which randomly assigned 916 patients

with hormone receptor– positive to letrozole 2.5 mg (n 458) or tamoxifen 20 mg (n 458) daily until disease progression.

This study documents the superiority of letrozole over tamoxifen in postmenopausal women with breast cancer including the degree of abnormal uterine bleeding among patients.

This can be explained by the longer duration and the larger sample of this study than our study as this study extended for 5 years while our study is only for 6 months.

The present study showed that there was no statistically significant difference between tamoxifen and letrozole groups regarding increased endometrial thickness either after 3 and 6 months of treatment. These results were inconsistent with the study done by Ho Sung Kim et al., 2008 in which A retrospective review was performed on 207 patients who had taken Tamoxifen or Anastrozole, as adjuvant hormonal therapy after breast cancer surgery between January 2003 and December 2006. Gynecologic surveillance constituted of ultrasonographic exam of the endometrial thickness and ovarian cyst formation. The patients were classified into three groups and analyzed; premenopausal/postmenopausal women receiving tamoxifen and women receiving anastrozole demonstrating that the endometrial thickness is accumulative effect of prolonged use of tamoxifen unlike aromatase inhibitors which does not increase the endometrial thickness

This may be due to the prolonged period of that study unlike our study which extended for only 6 months.

The present study showed that there was statistically significant difference between tamoxifen and letrozole groups regarding hemoglobin value in patients after 3 and 6 months of treatment as the values of hemoglobin decreased in tamoxifen group of patients. These results were consistent with the study done by Alan S. Coates et al.,2007 in which 4922 of the 8,028 postmenopausal women with receptor positive early breast cancer were randomly assigned (double-blind) to 5 years of continuous adjuvant therapy with either letrozole or tamoxifen; the remainder of women were assigned to receive the agents in sequence.

The present study showed that there was no statistically significant difference between tamoxifen and letrozole groups regarding abnormal uterine bleedingeither after 3 and 6 months of treatment. These results were inconsistent withthe study done by Henning Mouridsen et al. [14] which randomlyassigned 916 patients with hormone receptor– positive to letrozole 2.5 mg (n 458) or tamoxifen 20 mg (n 458) daily until disease progression. Thisstudy documents the superiority of letrozole over tamoxifen in postmenopausal women with breast cancer including the degree of abnormal uterine bleeding among patients. This can be explained by the longer duration and the larger sample of this study than our study as this study extended for 5 years while our study is onlyfor 6 months.

Summary and Conclusion

The present study aimed to compare the effect of both Tamoxifen andLetrozole as adjuvant treatment therapy in hormonal response breast cancer regarding abnormal vaginal bleeding, increased endometrial thickness and decreased hemoglobin value. The results of the present study showed that there was no significantdifference between Tamoxifen and Letrozole groups regarding age, age at menarche and medical, surgical& family history. It also showed that endometrial thickness at different follow up times was non-significantly more frequent in

Tamoxifen group than in Letrozole group, vaginal bleeding at different follow up times was non-significantly more frequent in Tamoxifen group than in Letrozole group. The results of the present study showed that no significant difference between Tamoxifen and Letrozole groups regarding baseline hemoglobin. Hemoglobin in months 3 and 6 were lower in Tamoxifen group than in Letrozole group, but the differences were statistically significant only in month-6. Hemoglobin reductions in months 3 and 6 were significantly higher in Tamoxifen group than in Letrozole group.

The results of the present study showed that iron tablets were non-significantly needed more frequent in Tamoxifen group than in Letrozole group at months 3 and 6, hemostatic drugs were non-significantly needed more frequent in Tamoxifen group than in Letrozole group at months 3 and 6. The results of the present study showed that dilatation and curettage was non-significantly more frequent in Tamoxifen group than in Letrozole group. All cases were at month-6 in both groups. Malignancy non- significantly found only in Tamoxifen group. The results of the present study showed that hysterectomy was non-significantly occurred only in Tamoxifen group. All of them needed at month-6. The results of the present study showed that mortality was not recorded in either group.

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