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THE EFFECT OF LEVONORGESTREL INTRAUTERINE SYSTEM ON ENDOMETRIUM IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER ON TAMOXIFEN THERAPY

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SUMMARY

Objective: *To evaluate the effect of levonorgestrel releasing intrauterine device on endometrium in postmenopausal women with breast cancer on tamoxifen therapy.*

Design: *A prospective randomised controlled study*

Setting: *Sisli Etfal Training and Research Hospital, Second Gynecology and Obstetrics Clinic, Istanbul*

Patients: *Thirty-four asymptomatic postmenopausal women, with uteruses, operated for breast cancer, on tamoxifen therapy for at least one year.*

Interventions: *Levonorgestrel intrauterine systems were applied to 17 subjects (study group). Main outcome measures: At 1. 3. 6. and 12. months of study, endometrial thickness and anteroposterior diameter of uterus was measured, and vaginal bleeding was scored as 0,1,2 and 3 when bleeding was respectively as 'spotting, minimal, mild or heavy'. Endometrial biopsies were repeated at the end.*

Results: *There was no difference between the groups with regard to age, gravity, parity, plasma hormone levels, duration of menopause, time passed till diagnosis of breast cancer and duration of tamoxifen use ($p>0.05$). For all time intervals, there was no difference in the anteroposterior diameter of uterus and endometrial thickness between the groups. However, in the study group, there was a significant decrease in anteroposterior diameter between 1. and 12. months of study ($p<0.05$) and a meaningful decline in endometrial thickness beginning from the third month ($p<0.001$). Vaginal bleeding declined significantly ($p<0.0001$). At the end of one year, the endometrial biopsies in the study group revealed 100% decidual reaction.*

Conclusion: *Levonorgestrel intrauterine system is a new preventive measure against undesirable agonistic effects of tamoxifen on endometrium.*

Key words: *breast cancer, endometrium, levonorgestrel releasing intrauterine device, tamoxifen,*

ÖZET

Tamoksifen Tedavisi Alan Meme Kanserli Postmenopozal Kadınlarda Levonorgestrel İntrauterin Sistemin Endometriyum Üzerine Etkisinin İncelenmesi

Amaç: *Tamoksifen alan meme kanserli postmenopozal kadınlarda levonorgestrel intrauterin sistemin endometriyum üzerine etkisinin incelenmesi.*

Planlama: *Prospektif randomize kontrollü çalışma.*

Ortam: *Şisli Etfal Eğitim ve Araştırma Hastanesi 2. Kadın Hastalıkları ve Doğum Kliniği, İstanbul.*

Hastalar: *Otuzdört asemptomatik postmenopozal, meme kanseri nedeniyle opere olmuş, en az bir yıldır tamoksifen tedavisi alan, uterusları olan hastalar.*

Girişim: *: Levonorgestrel intrauterin sistem 17 olguya uygulandı (çalışma grubu).*

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Değerlendirme parametreleri: *Çalışmanın 1. 3. 6. ve 12. aylarında, endometriyal kalınlık ve uterus ön-arka çapı ölçüldü ve vaginal kanama miktarı 'lekelenme, minimal, orta veya ağır' olacak şekilde sırasıyla 0,1,2 ve 3 olarak skorlandı. Çalışma sonunda endometriyal biyopsiler tekrarlandı.*

Sonuç: *Çalışma ve kontrol grubu arasında yaş, gravida, parite, plazma hormon düzeyleri, menopoz süresi, meme kanser tanısından sonra geçen süre ve tamoksifen tedavi süresi açısından fark yoktu ($p>0.05$). İncelenen tüm zaman dilimlerinde, gruplar arasında uterus ön-arka çapı ve endometriyal kalınlık farkı yoktu. Ancak, çalışma grubunda, 1. ve 12. aylar arası uterus ön-arka çapında anlamlı bir azalma oldu ($p<0.05$) ve 3. aydan başlayarak endometriyal kalınlıkta anlamlı bir incelme gözlendi ($p<0.001$). Vaginal kanama anlamlı derecede azaldı ($p<0.0001$). Bir yılın sonunda, çalışma grubundaki endometriyal biopsilerde %100 desidual reaksiyon izlendi.*

Yorum: *Levonorgestrel intrauterin sistem, tamoksifen tedavisinin endometriyum üzerindeki istenmeyen etkilerini önlemede yeni ve etkili bir yöntemdir.*

Anahtar kelimeler: *endometrium, levonorgestrel releasing intrauterine device, meme kanseri, tamoxifen*

INTRODUCTION

For the last 25 years tamoxifen is being used to decrease the incidence of invasive breast cancer and as a chemoprotective agent in healthy women with a high risk of breast cancer[1,2]. However, as a selective estrogen receptor molecule, the effect of tamoxifen on breast and endometrium is opposite; that is, it shows proliferative effect on endometrium. In postmenopausal women on tamoxifen therapy for more than two years, endometrial proliferation, hyperplasia, reactivation of endometriosis, rapid growth of uterine leiomyomas, adenomyosis, endometrial polyps, endometrial carcinoma and sarcoma were reported[3-6] Ineffective screening methods have led the way to various researches about antagonization of estrogenic effects of tamoxifen. Different systemic and local agents are promising hope. One of these agents is levonorgestrel intrauterine system (LNG-IUS), a progesterone releasing intrauterine system used as a contraceptive method in heathy individuals and especially in premenopausal women with breast cancer. In this study, we evaluated the effect of LNG-IUS in asymptomatic postmenopausal women on tamoxifen therapy.

MATERIALS AND METHODS

Thirty-four asymptomatic postmenopausal women, operated for breast cancer, on tamoxifen therapy for at least one year, with uteruses were recruited into study. All subjects entered the study by signing an informed consent form. The study was approved by the Ethics Committee of Sisli Etfal Training and Research Hospital.

The study group was composed of 17 subjects to whom LNG-IUS was applied. Seventeen, asemptomatic postmenopausal women taking tamoxifen made up the control group. One year of follow-up was planned. Exclusion criteria were submucosal myoma, adnexal masses, bleeding diathesis, other malignancies, uterine cavity length <4cm. in axial plane, refusal for application of LNG-IUS. Menopause was defined as serum estradiol level <50 pg/ml since tamoxiphene has a suppressive effect on gonadotrophines and patients might be amenorrheic due to therapies received for breast cancer.

Age, past medical histories, duration of menopause, genitourinary symtoms, pathological diagnosis, type and duration of therapy for breast cancer were all questioned. Pre-study assessment included gynecologic examination, cervical smear, transvaginal ultrasonography (TV-USG) and saline infusion sonography (SIS). Aloka SSD 1100-Flexus with a probe of 5 MHz transducer was used for sonographic examinations. Any pathology identified by SIS was furher evaluated by hysterescopy.

In the study group, LNG-IUS application was performed after endometrial sampling by pipelle and sharp curettage.

In the control group, only when endometrium was > 6 mm. thick or there was vaginal bleeding, endometrial biopsy was done.

During the study, anteroposterior diameter of the endometrium and uterus was measured at sagital view at 1. 3. 6. and 12. months in both groups. Endometrial biopsies were

repeated at the end of one year in the study group by pushing the pipelle gently next to the intrauterine system into the cavity.

Subjects with LNG-IUS were given charts to mark the amount of vaginal bleeding daily. Bleeding was classified as spotting, mild, moderate and heavy and was scored as 0, 1, 2 and 3 respectively.

Graph Pad Prisma V.3 package programme was used for statistical analysis. Friedman, Mann-Whitney-U, Chi-square, Fischer and Dunn's multiple comparison tests were used for statistics. P<0.05 was considered as significant and confidence interval was considered as %95.

RESULTS

The demographic characteristics are given in Table I.

Table I: *Some demographic characterictics of subjects.*

	Study Group (n=17)	Control Group (n=17)	MW	p
Age	47.35±8.59	49.88±8.69	105.5	**>0.05**
Gravidity	4.69±2.06	4.82±2.77	127.5	**>0.05**
Parity	3.19±1.56	3.18±1.29	129.0	**>0.05**
Number of abortion	2.18±0.87	2.55±2.16	55.**0**	**>0.05**
FSH (mIU/ml)	30.94±9.86	26.12±8.30	95.5	**>0.05**
LH (mIU/ml)	17.71±5.97	14.00±4.78	90.5	**>0.05**
E2(pg/ml)	32.47±11.65	30.18±10.93	107.5	**>0.05**
Duration of menopause (month)	52.29±61.98	63.47±70.55	103.0	**>0.05**
Duration of diagnosis of breast cancer (month)	31.47±12.64	33.47±13.48	128.0	**>0.05**
Duration of tamoxifen therapy (month)	27.76±12.07	30.94±13.33	120.0	**>0.05**

The type of therapy for breast cancer is shown in Table II.

Table II: *History of chemotherapy and radiotherapy*

		Study Group	Control Group	
Chemotherapy	(-)	1 (5.9%)	0	
	(+)	16 (94.1%)	17 (100%)	**P>0,05**
Radiotherapy	(-)	6 (35.3%)	1(%5,9)	
	(+)	11 (64.7%)	16 (94.1%)	**P<0,05**

The results of pre-study SIS is given in Table III. In general, polyp was observed in 32.3% (n=11) patients. Since there was no submucous myoma, this parameter was not evaluated.

Table III: *Result of pre-study SIS*

		Study Group	Control Group	
	Normal	12 (%70,6)	11 (%64,7)	
SIS	Polyp	5 (%29,4)	6 (%35,3)	**p>0,05**

The anteroposterior diameter of the uterus is shown in Table IV. There was no significant difference between the groups for all time intervals evaluated. The inter-group evaluation of the LNG-IUS group revelaled significant decrease especially between 1. and 12. months of study (p<0,05).

Table IV: *Anteroposterior diameter of uterus (given as mm)*

	Study Group (n=17)	Control Group (n=17)	MW	P
0. month	44.88±5.79	42.18±5.67	102.5	**>0.05**
1.month	46.00±5.70	42.76±6.67	95.5	**>0.05**
3.month	45.18±5.00	43.06±6.47	105.5	**>0.05**
6.month	44.75±5.25	43.18±6.50	112.5	**>0.05**
12.month	42.57±4.31	43.06±6.59	118.0	**>0.05**
P	**<0.05**	**>0.05**		

The comparision of endometrial thickness is given in Table V. Only for the first month, there was a significant difference between the groups (p<0,01). In the LNG-IUS group, there was a meaningful intergroup decrease in endometrial thickness evident from the third month (p<0.001) and which was greatest when 1. and 12.months were compared (p<0,0001).

Table V: *Endometrial thickness*

	Study Group (n=17)	Control Group (n=17)	p
0.month	9.56±3.78	7.96±4.13	**>0.05**
1.month	8.76±2.70	6.59±2.17	**<0.01**
3.month	7.38±3.23	6.47±2.12	**>0.05**
6.month	8.13±5.84	7.35±4.40	**>0.05**
12.month	5.24±0.78	7.35±4.91	**>0.05**
P	**<0.0001**	**>0.05**	

The vaginal bleeding score in the LNG-IUSgroup is given in Table VI. LNG-IUS was applied for 12.47±2.29 months. There was a significant decrease in the bleeding scores (p<0,0001). In two subjects (%11,8) with no

decrease, SIS was performed and then LNG-IUS was removed. In one, bleeding stopped after removal of LNG-IUS. In this patient, new polys appeared afterwards. In the other, hysterectomy had to be performed.

Table VI: *Vaginal bleeding score in the LNG-IUS group*

Months	Study Group (n=17)
1	2,12±0,99
3	2,24±1,25
6	0,82±1,29
12	0,29±0,85
Fr	25,21
P	**<0,0001**

All subjects in the study group and 10 patients with vaginal bleeeding or with endometrial thickness > 6 mm in the control group went through biopsy. The results of endometrial biopsies are shown in Table VII. There was no difference between the groups in 0.month biopsies. At the end of 12. months, since there were very different results between the groups, we were unable to use statistics. Therefore, the results are given as percentages. At the end of 12 months, in the study group, decidual reaction was evident (100%) and one polyp occured in each group. In the control group as different from the study group, one hyperplasia was observed; however, this was insignificant. Insufficient material seemed to be evaluated as inactive endometrium. Therefore, in the LNG-IUS group, probaly due to abundant decidual reaction, this problem seems to be somehow resolved.

Table VII: *Endometrial biopsies*

		Study Group	Control Group	
	Estrogenic effect	8 (47.1%)	5 (50%)	
	Inactive endometrium	7 (41.2%)	3 (30%)	
0. month	Endometrial polyp	2 (11.8%)	2 (20%)	**p>0,05**
		Study Group	Control Group	
	Decidual reaction	17 (100%)	0 (0%)	
	Estrogenic effect	0 (0%)	5 (50%)	
	Endometrial hyperplasia	0 (0%)	1 (10%)	
	Inactive endometrium	0 (0%)	3 (30%)	
12. month	Endometrial polyp	1 (5.9%)	1 (0%)	

DISCUSSION

The systemic and local effects of LNG-IUS as a contraceptive method have been proven[3-6]. Moreover, it is being used in hormone replacement therapy (HRT) combined with oral and transdermal estrogen. Our study focuses on the antagonistic effects of LNG-IUS on endometrium in women receiving tamoxifen therapy. Screening of genital system in patients using tamoxifen as an adjuant therapy is mandatory for three reasons [7]. First, breast and endometrium cancers have common risk factors and they may occur together. Second, metastases of breast cancer to the ovaries can be detected by a careful sonographic examination. Third, tamoxifen increases the incidence of both benign and malignant diseases of the uterus[8]. This last reasons constitudes the basis of our study and LNG-IUS is used to counteract the estrogenic effects of tamoxifen on endometrium.

The incidence of endometrial hyperplasia and cancer in patients using tamoxifen is given respectively as 1.3-20% and 0-8% in various reports[9-11]. The incidence of endometrial polyps in breast cancer patients on tamoxifen threapy is %8-36 while in patients not taking the drug is %0-10[12]. Some authors advocated abnormal endometrial volume as a result of tamoxifen [13].

There is no concensus in literature about the time needed for development of endometrial pathologies. The relative risk for endometrial cancer was said to depend on duration of treatment and cumulative dose of the drug[12]. De Muylder reported this time as minimum of 15 months and average of 24 months[14]. In our study, we could not found a significant relationship between duration of tamoxifen use and endometrial thickness and uterus size, but all endometrial pathologies were seen after 25 months of therapy.

In our study, we observed increased incidence of benign endometrial pathologies in postmenopausal women on adjuant tamoxifen therapy. At the beginning, we identified by SIS 32.3% polyp in both study and control groups respectively on tamoxifen therapy for 27.76±12.07 and 30.94±13.33 months. When compared to other postmenopausal women, this incidence is significantly high. We did not find any endometrial hyperplasia and cancer at the beginning. Likewise, Gardner et al. showed only benign uterine changes in

52 women who had had at least 1 year of adjuant tamoxifen treatment[10]. However, at the end of 12-months-study, one hyperplasia developed in the control group. Gardener et al. found no hyperplasia in 47 women on adjuant tamoxifen treatment with LNG-IUS at the end of one year[10].

The systemic and local effects of LNG-IUS as a contraceptive are shown and in HRT it is being used to protect the endometrium[15-18]. Likewise its use in patients on tamoxifen treatment is considered[10]. The theraupeutic effects of LNG-IUS on endometrium is evident starting from the 3.month of therapy. The size of endometrial glands decrease, a widespread decidualization in stroma begins and mucosa gets thinner[19]. The changes in endometrium is full thickness and homogenous regardless of the area of sampling, the closeness of the endometrium to the ultrasound or the distrubution of hyperplasia at the start[20].

In our study, LNG-IUS was applied to 17 subjects. Endometrial thickness, anteroposterior diameter of the uterus and endometrial biopsies were evaluated. There was no difference between the groups in duration of menopause, time past till diagnosis of breast cancer, duration of tamoxifen use, and the results of SIS and biopsy at the start of study.

We observed significant decrease in the anteroposterior diameter of the uterus in the LNG-IUS group starting from the first month of study in contrast to the findings of Gardner (10). We found no difference in endometrial thickness between the groups; however, in the LNG-IUS group, there was a significant thinning in accordance with the study of Gardner et al. Intrauterine device may affect the endometrial volume because there was a significant fall in endometrial thickness at the end of 12 months. There was no such as difference in the control group.

Ideal screening method to evaluate the endometrium in tamoxifen using patients is also controversial. Even though ultrasonography is easy to use, its sensitivity and specifity in these patients is questionable[21]. Intracavitary pathologies can more easily be identified and localized by SIS[12]. Since endometrial carcinomas seen in tamoxifen users are usually focal, sensitivity of dilatation and curettage is very low[22]. Therefore, hysterescopy or SIS in addition to ultrasonography are very important for determining the site of biopsy. Cohen reported that till an ideal screening test was developed, for symtomatic patients hysterescopy and/or biopsy and for asymptomatic patients USG or biopsy should be performed[22,23].

The most frequent complaint of the subjects was vaginal bleeding especially during the first three months of therapy as stated in our reports[10,16,17,24]. Even though the amount of bleeding decreased during the 12 months study period, the subjects were emotionally negatively affected. However, there was no severe bleeding in the study group. Gardner also reported decreased bleeding in women on adjuant tamoxifen therapy with LNG-IUS at the end of one year[10].

In accordance with literature, at the end of 12 months, there was widespread decidualization in all patients in the control group, and in one there was reoccurence of polyp[25]. However, in this one patient, there was also decidualization. Gardner et al. also showed uniform decidual response in all women on adjuant tamoxifen therapy with LNG-IUS at the end of one year[10]. Even though at the beginning, we performed curettage for preexisting polyps and afterwards we applied LNG-IUS, in only one subject polyp developed. This can be explained as either we missed it before so that it continued to grow or it is due to de novo formation which means that the system can not prevent de novo formation. Gardner et al. reported the incidence of polyp as 2% after one year of LNG-IUS[10].

As it is clearly stated in literature, the greatest difficulty in patients on tamoxifen treatment was insufficient endometrial sampling independent on the technique used[26,27]. In our study, we used pipelle biopsy without taking out the LNG-IUS. This might be questioned. However, endometrial biopsy with the Pipelle was shown to be superior to other endometrial techniques in the detection of endometrial carcinoma and atypical hyperplasia. The accuracy of the Pipelle ishigher in postmenopausal women compared with premenopausal women[28]. Moreover, it was suggested that pipelle sampling combined with sonographic measurement of endometrial thickness was an acceptable, less invasive alternative to hysteroscopy and D&C as a first-line investigation in the management of post-menopausal bleeding[29]. In subjects with LNG-IUS, the handicap of insufficient endometrial sampling independent on the technique used was partly overcome probably by softening of the uterus as a result of decidualization. We believe that levonorgestrel intrauterine system is a new preventive measure against undesirable agonistic effects of tamoxifen on endometrium. However, since

the systemic effects of LNG-IUS in breast cancer patients are still not known, more prospective and widespread studies should be carried out to fully enlighten the effectiveness of LNG-IUS in antoganization of effects of tamoxifen.

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