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RESEARCH ARTICLE

Tibolone: An Emerging Option as Hormone Replacement Therapy and Its Comparison with Vaginal Estrogen in Relieving Urogenital Symptoms

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ABSTRACT

Introduction: To study efficacy and side effects of Tibolone in alleviating postmenopausal symptoms and compare it with vaginal estrogen.

Materials and methods: This prospective study was done on 100 postmenopausal women with amenorrhea of more than 1 year. All patients had one or more urogenital complaints. They were randomly assigned to receive Tibolone tablet 2.5 mg once daily (50 cases; group I) and vaginal estrogen (50 cases; group II). Both groups were compared at 1 and 6 months after starting treatment for genitourinary complaints. Chi-square test was used for comparison. A p-value of 0.05 was considered as significant.

Results: After 1 month of t/t, Tibolone was slightly better in relieving genital symptoms, while significantly improved dyspareunia and dryness in vagina after 6 months as compared with estrogen. After 6 months both groups showed clinically marked improvement in dysuria, frequency, and urgency.

Conclusion: Tibolone was better than estrogen in relieving dyspareunia and dryness in vagina. Both are equally effective in relieving urogenital symptoms, decreasing the recurrence rate of vaginal and urinary infections, and bringing out improvement in general well-being. Tibolone causes less nausea, edema, breakthrough bleeding as compared with estrogen.

Keywords: Dyspareunia, Estrogen, Tibolone, Urogenital symptoms, Vaginal dryness.

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INTRODUCTION

Menopause is defined as the time of cessation of ovarian function resulting in permanent amenorrhea (Speroff L; Lippincott Williams & Wilkins; 2004). It is not a disease or illness but a natural event that naturally occurs in women between age 45 and 55. During this period, the ovaries stop releasing eggs and produce less of the female hormones estrogen and progesterone. Some of the symptoms commonly seen during menopause are irregular bleeding, hot flushes, night sweats, palpitations, vaginal dryness, dyspareunia, leukorrhea, urinary incontinence, frequency, urgency, nocturia and dysuria, etc. Other changes include skin laxity, dry lusterless skin, skeletal aches and pains, and mood swings/irritability.[1]

Hormone replacement therapy (HRT) is the augmentation of postmenopausal woman's low hormone level with estrogen or a combination of estrogen and a progesterone standard therapy of 0.625 mg/day of conjugated estrogens (such as premarin), but the dose can range from 0.3 to 1.25 mg/day.

Tibolone has been classified as a selective tissue estrogenic activity regulator (STEAR). It relieves vasomotor symptoms as well as positive effects on sexual well-being and mood and vaginal atrophy and urogenital symptoms. It improves bone marrow density, reduces the risk of breast discomfort and mammographic changes, endometrium proliferation, and venous thromboembolic events.[2]

OBJECTIVES

- To study the efficacy of Tibolone in relieving urogenital symptoms.
- To compare the effects of Tibolone and vaginal estrogen in urogenital complaints.
- To study and compare the side effect of both drugs.

MATERIALS AND METHODS

The study was carried out on 100 postmenopausal females with amenorrhea more than 1 year or who had pan-hysterectomy at least 1 month back, with one or more urogenital complaints. The patients were randomly assigned groups:

Group I – Tibolone (2.5 mg/day) (50 cases each)
Group II – Vaginal estrogen cream (0.625 mg/day – conjugated estrogen cream).

Oral progesterone 5 mg/day was added to last 12 days of the cycle in natural menopausal cases, and compared at 1 and 6 months, for relief in urogenital complaints. The study duration was 1 year and was approved by Ethical Committee of the hospital.

Inclusion Criteria

- Genital symptoms: Pain, dyspareunia, discharge, burning feeling, dryness in vagina.
- Urinary symptoms: Dysuria, frequency, urgency, nocturia, urinary incontinence.

Exclusion Criteria

- Patients with undiagnosed vaginal bleeding, genital neoplasia, breast neoplasia, or history of carcinoma breast in family.
- Cerebrovascular diseases, cardiovascular diseases, thromboembolic diseases, severe liver diseases.
- History of diabetes mellitus, epilepsy, pelvic inflammatory disease, migraine, herpes, high cholesterol level.

After written consent of each case, patients were divided in two groups: Each of 50 patients. Group I received oral Tibolone tablet 2.5 mg/day. Group II received oral premarin tablet 0.625 mg/day and oral progesterone 5 mg/day for last 14 days of the cycle in natural menopausal cases. Patients were evaluated after 1 and 6 months of therapy. Chi-square test was used for comparison.

Investigation carried out were: Hemoglobin, total leukocyte count, differential leukocyte count, blood sugar, liver function test, renal function test, S. cholesterol, complete urine examination – routine and microscopic, urine culture/sensitivity, high vaginal swab culture, and sensitivity.

Estrogen (also estrogens) is a group of steroid compounds produced primarily by developing follicles in the ovaries, the corpus luteum, and the placenta. Some estrogens are also produced in smaller amounts by other tissues, such as liver, adrenal glands, and the breast. These secondary sources of estrogen are especially important in postmenopausal women. As estrogen levels are declining as soon as approaching menopause. So we need it to replace by synthetic estrogen or estrogen and progesterone combined therapy for relieving postmenopausal symptoms.[3]

Tibolone is a gonadomimetic synthetic steroid, and it has tissue specific effects. After oral ingestion, Tibolone is converted to three active metabolites: The 3α-OH and 3β-OH have estrogenic effects on bone, vagina, and climacteric symptoms, while the Δ^4 isomer has progestogenic and androgenic properties and prevents stimulation of the endometrium.[4]

RESULTS

Maximum number of cases were between 45 and 49 years of age in both groups. Age of menopause has reduced due to increased incidence of pan-hysterectomy at an early age. In Tibolone group, 40% of cases belong to natural and 60% from surgical type of menopause while in estrogen group also maximum cases belong to surgical type of menopause (68%). Women from urban area were (60%) more aware of menopausal problems than rural area (40%) in both groups. Maximum number of women presented with their symptoms at 12 months to 1 month duration of menopause in both groups (Table 1).

Table 2 shows maximum of 65% cases got relief in pain and 80% cases got relief in dyspareunia in Tibolone group, while 60% of cases in estrogen group for both symptoms. Relief in discharge and burning feeling was more in estrogen group than in Tibolone group: 60% *vs* 30% and 65% *vs* 60% respectively, after 1 month of therapy. Dryness in vagina was relieved in 7 cases out of 10, i.e., 70% in Tibolone (group A), while in 46% in estrogen (group B).

Dysuria improved in 65% cases in both groups. Frequency and urgency relieved clinically better in Tibolone group. Nocturia relieved in 50% cases while incontinence was improved completely in our study after 1 month of therapy in group A. Relief from all symptoms are comparable and p value was nonsignificant.

Table 3 shows improvement after 6 months. Patient in Tibolone group reported significant relief in dyspareunia

Table 1: Patients profile

	Tibolone (A)		*Estrogen (B)*	
	Total no. of cases	*%*	*Total no. of cases*	*%*
Age				
35–39 years	9	18	10	20
40–44 years	7	14	8	16
45–50 years	12	24	13	26
50–54 years	10	20	10	20
55–59 years	9	18	6	12
>60 years	3	6	3	6
Type of menopause				
Natural	20	40	16	32
Surgical	30	60	34	68
Duration of menopause				
6–12 months	8	16	10	20
12–18 months	17	34	16	32
18–24 months	15	30	15	30
>24 months	10	20	9	18
Rural or urban				
Rural	18	36	20	40
Urban	32	64	30	60

Table 2: Distribution of cases according to complete relief in urogenital complaints after 1 month

	Tibolone			*Estrogen*			χ^2	*p-value*
Genital symptoms								
Pain (G1)	20	13	65	18	11	61.11	0.06	0.8
Dyspareunia (G2)	15	12	80	10	6	60	1.19	0.27
Discharge (G3)	10	3	30	10	6	60	1.81	0.17
Burning feeling (G4)	15	9	60	20	13	65	0.09	0.76
Dryness in vagina (G5)	10	7	70	15	7	46.6	1.8	0.18
Urinary symptoms								
Dysuria (U1)	20	13	65	17	11	64.7	0.034	0.05
Frequency (U2)	19	12	63	21	12	57.14	0.15	0.698
Urgency (U3)	13	8	62	12	6	50	0.337	0.561
Nocturia (U4)	2	1	50	1	0	0	0.44	0.5
Incontinence (U5)	1	1	##	1	0	0	0.187	0.665

Table 3: Distribution of cases according to complete relief in urogenital complaints after 6 months

	Tibolone			*Estrogen*			χ^2	*p-value*
Genital symptoms								
Pain (G1)	20	15	75	18	14	77.77	0.04	0.841
Dyspareunia (G2)	15	15	100	10	7	70	5.11	0.023*
Discharge (G3)	10	7	70	10	8	80	0.05	0.624
Burning feeling (G4)	15	11	73.33	20	15	75	0.012	0.912
Dryness in vagina (G5)	10	10	100	15	7	46.66	0.09	0.024*
Urinary symptoms								
Dysuria (U1)	20	16	80	17	14	82.35	0.033	0.85
Frequency (U2)	19	15	78.94	21	18	85.71	0.316	0.574
Urgency (U3)	13	9	69.23	12	9	75	0.103	0.748
Nocturia (U4)	2	1	50	1	0	0	0.44	0.5
Incontinence (U5)	1	1	100	1	1	100	–	–

(100) and dryness of vagina (100) at 6 months of treatment, while in estrogen group there is 70% improvement in dyspareunia and 46% in dryness of vagina was seen. Other genital symptoms relieved markedly in both groups. Moreover, relief in urinary complaints at 6 months was better in estrogen group.

In Tibolone group, 9 patients had urinary infection and the microorganisms responsible were *Staphylococcus*, *Streptococcus*, and *Escherichia coli*. At 1 month of therapy, 2 patients were found infected, 1 patient with *Streptococcus* had now become infected with Klebsiella. After 6 months, 1 new patients was found infected with *Staphylococcus*. In estrogen group, 9 patients were infected before therapy with *Staphylococcus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Candida*. At 1 month of therapy, one new patients not previously infected had positive urine culture for *Staphylococcus*. At 6 months of therapy, none of the patients in estrogen group had urinary infection.

Table 4 also shows the microorganisms that were isolated in vaginal swab culture from patients in both

Table 4: Culture flora isolated in infected patients

Microorganism	*Tibolone*			*Estrogen*		
Urinary flora	*Before 1 month*	*After 1 month*	*After 6 months*	*Before 1 month*	*After 1 month*	*After 6 months*
Staphylococcus	3	–	1	2	1	–
Streptococcus	2	1	–	2	–	–
Escherichia coli	4	–		3	–	–
Klebsiella	–	1	–	1	–	–
Candida	–	–	–	1	–	–
Vaginal flora						
Staphylococcus	1	–	–	2	–	–
Streptococcus	2	1	–	1	1	–
Escherichia coli	5	1	1	3	–	–
Klebsiella	1	–	–	1	–	–
Candida	1	–	–	–	–	–

Table 5: Adverse effects of both drugs

	Tibolone		*Estrogen*	
Adverse effect	*No. of patients*	*%*	*No. of patients*	*%*
Nausea	7	14	9	18
Edema	10	20	10	20
Breast tenderness	3	6	9	18
Breakthrough bleeding	3	6	8	16
Skin greasiness		–		
Increase in hair growth	–	–	–	–

groups. In the Tibolone group, the organisms present in 10 patients before therapy included *Staphylococcus aureus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Candida albicans*. After 1 month of therapy, one case found infected with *Streptococcus* and one with *E. coli*. At 6 months of therapy, one patient was found infected by *E. coli*. In estrogen group, 7 patients were infected before therapy with *Staphylococcus*, *Streptococcus*, *E. coli*, and *Klebsiella*. At 1 month of therapy, one patient was found infected with *Streptococcus*, who previously had no infection. And at 6 months none of the patient was found infected. The comparison of both groups showed no statistically significant difference and were equally effective in relieving recurrence of vaginal and urinary infection in postmenopausal women.

Table 5 compares the side effects of Tibolone and estrogen group. Nausea was seen in 14% cases in Tibolone group and 18% in estrogen group. Edema was seen in 20% cases in both groups. Breast tenderness was observed in 6% cases of Tibolone and 16% of estrogen group. On comparison, Tibolone has less side effect than estrogen group.

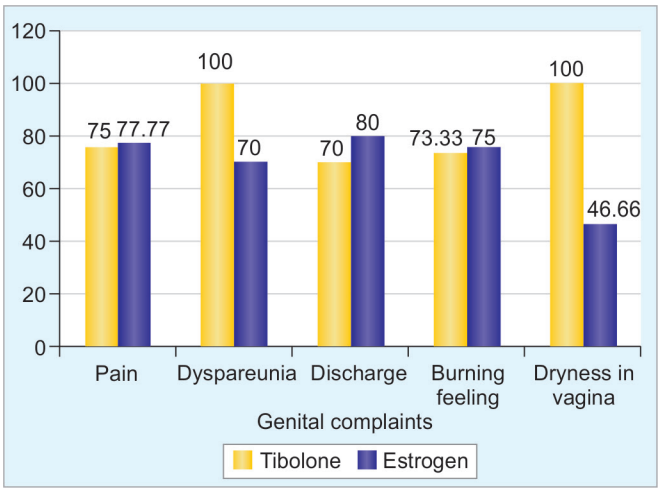
DISCUSSION

Menopause typically (but not always) occurs in woman's midlife, during their late 40s or early 50s, and signals the end of the fertile phase of a woman's life. Menopausal symptoms affect about 70% of women approaching menopause. A recent increase in female longevity due to improvements in the standard of living and social care can be suggested as a possible reason for the reported increase of living of menopausal symptoms, in those cases where the physical, mental, and emotional effects of menopause are so strong enough that they significantly disrupt the everyday life of the woman experiencing them, and hence palliative medical therapy may be required.

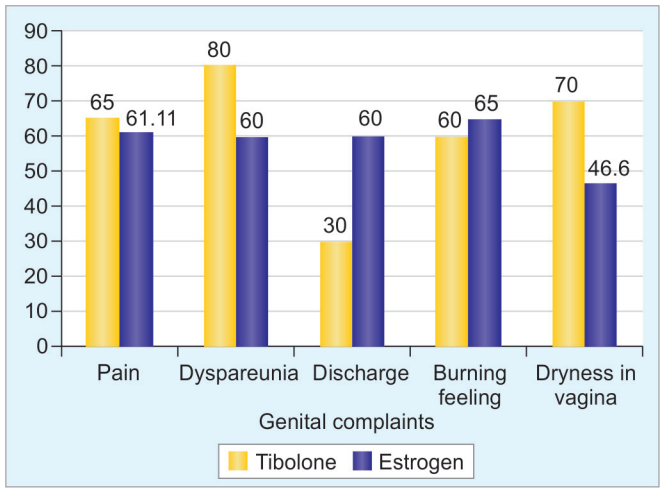
In present comparative study between Tibolone and estrogen regarding the relief of menopausal symptoms, both the groups were comparable in respect to mean age, residence, type of menopause, and total duration of menopause.

In our study, after 1 month of therapy clinical improvement in genital symptoms was 60 to 80% in Tibolone group while in estrogen it was around 60% (Graph 1). After 6 months, relief in dyspareunia ($p = 0.23$) and dryness of vagina ($p = 0.24$) was significantly improved with Tibolone group than with estrogen (Graph 2). Rymer et al[5] also showed significant symptomatic improvement in vaginal dryness, dyspareunia, sexual enjoyment, and libido in postmenopausal women taking Tibolone. Tibolone has been shown to reverse the vaginal atrophy (increase in karyopyknotic index and cell maturation value) and improve cervical mucus. Women treated with Tibolone have reported significantly less vaginal dryness, dyspareunia, and urinary symptoms.[6] Baracat et al[7] stated that women treated with conjugated equine estrogen (CEE)/ medroxy progesterone acetate (MPA) or Tibolone showed significant improvement in postmenopausal symptoms, including urogenital and sexual health symptoms.

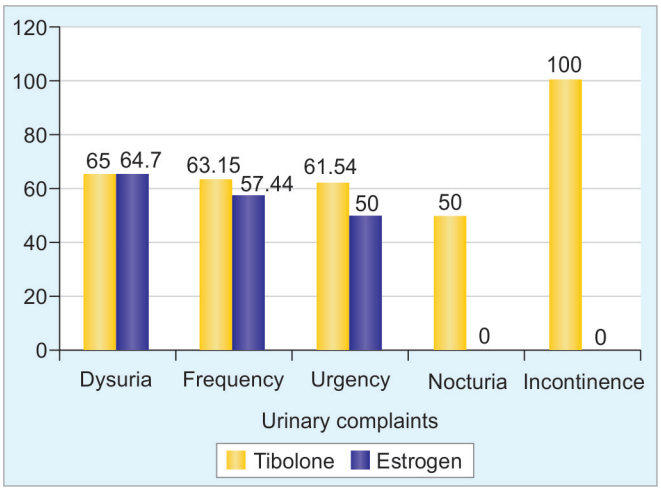
In our study when we observed improvement of the urinary symptoms at the end of 1 month, dysuria



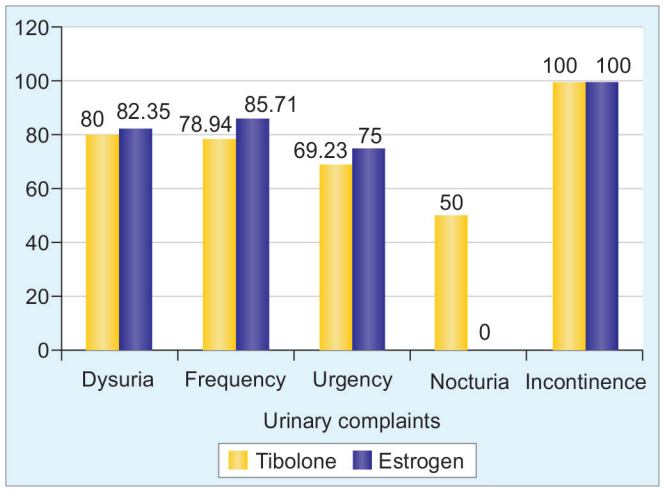
Graph 1: Distribution of patients according to degree of relief in genital symptoms after 1 month



Graph 2: Distribution of patients according to degree of relief in genital complaints after 6 months



Graph 3: Distribution of patients according to degree of relief in urinary complaints after 1 month



Graph 4: Distribution of patients according to degree of relief in urinary complaints after 6 months

was relieved significantly in both groups, i.e., 64% (Graph 3). Relief in urinary frequency was 63.15% in Tibolone as compared with estrogen 57.14%, similarly urgency in 61.54% in Tibolone as compared with estrogen 50%. Nocturia relieved 50% in Tibolone and none in estrogen, whereas incontinence relieved 100% in Tibolone at the end of 1 month. Swanson et al[8] showed significant reduction in nocturia compared with placebo at weeks 4, 8, and 12 and urinary urgency at 4 weeks. Urogenital symptoms are common and distressing but may be reversible with exogenous HRT.[9]

On comparing the beneficial effects of both Tibolone and estrogen groups, it was found that both are equally effective in relieving urogenital symptoms, decreasing the recurrence rate of vaginal and urinary infections and bringing out improvement in general well-being. A 1993 study by Raz and Stamm[10] also found that recurrent urinary tract infections were effectively prevented (0.5 *vs* 5.9 episodes per year) by postmenopausal treatment with HRT. Eriksen[11] found a significant reduction in incidence of urinary tract infection in treated women with HRT ($p = 0.008$).

In our study it was noted that there was less complain of breast tenderness and edema in cases receiving Tibolone. Modelska and Cummings[12] concluded that breast tenderness was reported more often with E_2/NETA than with Tibolone (p-value < 0.0001) and bleeding episode was reported more often with E_2/NETA than with Tibolone (p-value < 0.0001) in first 6 months treatment (Graph 4).

Hormone replacement therapy is essential not only in cases of urogenital symptoms or other climacteric symptoms but also as a prophylaxis for long-term consequences, especially after surgical menopause, when it should be started as early as 1 month after hysterectomy.

CONCLUSION

Tibolone differs from the other preparations in that it is not a combination of estrogen and progesterone but a single drug which combines the properties of both, as well as some of the properties of male sex hormones. The good thing about the Tibolone is that it does not stimulate lining of uterus. This means that if you start taking it at least 1 year after your periods have stopped, you will not get any monthly periods as you would with other hormonal treatments.

Tibolone was significantly better than vaginal estrogen cream in relieving dyspareunia and dryness in vagina. Both are equally effective in relieving urogenital symptoms, decreasing the recurrence rate of vaginal and urinary infections, and bringing out improvement in general well-being.

Tibolone cause less nausea, edema, breast tenderness, and breakthrough bleeding as compared with estrogen. Both the drugs improve the quality of life and health of Indian women in the sunset of their lives. To get more confirmatory and significant results, larger group of cases with long-term follow-up is required.

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