



Indian Menopause Society

Guideline Number 2 : August 2010

Tibolone for Postmenopausal Women

Background: In the last 5 to 7 years, after the publication of the Women's Health Initiative (WHI) data, Hormone Therapy (HT) has fallen into disrepute. This has been mainly due to the array of side effects, most importantly the fear of breast cancer both on the part of women themselves and clinicians. It is thus important now to determine the specific place of tibolone, a synthetic steroid with a unique clinical profile as a postmenopausal therapeutic option.

Pharmacology: Tibolone is a selective tissue estrogenic activity regulator (STEAR). It has estrogenic, progestogenic and androgenic properties. After oral administration, it is rapidly absorbed and metabolized into 3 active metabolites – a Delta 4 isomer and 3 alpha and beta hydroxy metabolites. The parent compound and these metabolites bind to a greater or lesser extent to steroid receptors and this is what gives Tibolone its tissue specific activity.¹

Action on Breast: Tibolone decreases the proliferation rate, promotes 17-beta hydroxysteroid dehydrogenase activity (a marker for epithelial cell differentiation) and increases apoptosis in normal human breast epithelial cells as well as breast cancer cells.² Tibolone displays a progestin profile or anti estrogenic action in breast cells.

Action on Endometrium : Tibolone induces endometrial atrophy by a tissue specific effect. It has a local progestogenic effect which minimizes the estrogenic effects of tibolone. On the lower genital tract, both karyopyknotic index and maturation index improve in women who are on tibolone, thus reversing the vaginal atrophy that takes place after the menopause, while maintaining an inactive endometrium³.

Action on Bone : Tibolone has an estrogenic effect on bone, thus inhibiting bone resorption by reducing osteoclastic activity. Bone mineral density has been shown to increase at both at the lumbar spine and upper femur. This has been observed even with half the conventional dose, i.e. 1.25 mg instead of 2.5mg. Fracture efficacy has now been added to the list of tibolone's documented bone benefits. Reduction in fracture risk (i.e. 50%) is greater than would be predicted from BMD change.⁴

Action on Lipids: Tibolone causes a decrease in triglycerides, total cholesterol, low-density lipoprotein (LDL) and lipoprotein (a) levels. However, it also lowers levels of

high-density lipoprotein (HDL) cholesterol, which has been a cause for concern. Studies have also found a decrease in fibrinogen and factor VII activity, increase in anti thrombin III and plasminogen with an overall trend towards increase in fibrinolytic activity with tibolone. Cardiovascular clinical outcomes from randomised controlled trials are not available yet.⁵

Vasomotor symptoms: Tibolone is effective in reducing episodes of flushing and sweating, perhaps the most immediate features of the menopause.⁶

Mood and Libido: Tibolone helps relieve insomnia and also increases beta endorphin and beta lipoprotein levels thus improving mood. The androgenic effect of tibolone helps to improve libido. The estrogenic effects on the vagina, decrease the vaginal dryness and decrease dyspareunia. The combined effects cause an overall improvement in mood, libido and sexual enjoyment.⁷ Asian women can be more reticent about discussing sexual dysfunction than Western women. As tibolone is more effective in improving sexual function than HRT women who experience related problems are likely to benefit from it.⁸

Other Effects: Tibolone has also been found to mitigate the menopause-related decline in muscle strength. Tibolone also increases lean body mass and significantly reduces the total body fat content.⁹

Tibolone has no significant effect on carbohydrate metabolism.¹⁰

Inconclusive Evidence: There is no conclusive end-point data on cardiovascular risk. Neither is there any data on the effect of tibolone on the central nervous system.

Tibolone in the Indian Context:¹¹ Tibolone is more expensive than conventional HT. Women here are particularly concerned about irregular bleeding and spotting, which is not a major issue with Tibolone.

Here, in India where Mammography is not easily available and expensive, it may be better to use a drug which does not increase the risks of breast cancer.

Hypertriglyceridaemia is the commonest lipid profile abnormality seen in Indian women. Tibolone definitely reduces the triglyceride levels.

An Indian study has shown an improvement in quality of life in women receiving Tibolone.¹²

Dosage : Tibolone is prescribed in a single daily dose of 2.5 mg orally. Recent data has shown a lower dose of 1.25 mg to be equally effective in many cases.

Side effects: As with most drugs, nausea is a common side effect on initiation of therapy, but reduces in a few weeks.

Breakthrough bleeding may also occur. It is best to initiate therapy after a minimum of twelve months amenorrhoea. Patients should be counseled and no investigations are required if spotting or slight bleeding occurs in the first three months of treatment.

Breast tenderness may occur, but is transitory.

Some patients have excessive weight gain.

Rarely, androgenic effects such as an increase in hair growth may occur.

Breast Cancer : Tibolone does not cause breast proliferation and does not increase the mammographic density of the breast. Estrogen on the other hand is known to stimulate breast tissue with an increased risk of breast cancer after long term therapy. Conventional hormone therapy is usually not prescribed to breast cancer survivors because of a fear of recurrence. A small study has shown that Tibolone does not reveal a negative impact on breast cancer outcome when given to breast cancer survivors.¹³

The Million Women Study concluded that current use of HRT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for estrogen- progestogen combinations than for other types of HRT. This was the first study to show an increased risk of breast cancer in tibolone users. The preferential prescription of tibolone in women at greater risk for breast cancer may explain the unexpected increase in breast cancer risk for tibolone users in the Million Women Study.¹⁴

LIBERATE, a randomized placebo-controlled clinical trial was designed to assess the safety and efficacy of tibolone when used for the relief of menopausal symptoms in patients with a history of breast cancer. It was stopped early as there was a trend for an excess of breast cancer recurrences in the group of women randomized to receive tibolone.¹⁵

Endometrial Cancer : The endometrial safety of tibolone has been questioned after a report from the Million Women Study showing an increased risk of endometrial cancer in women with last use of tibolone or estrogen alone. Tibolone appears to be selectively prescribed to women at increased risk of both endometrial and breast cancer. The Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES) results confirm previous findings that tibolone does not induce endometrial hyperplasia or carcinoma in postmenopausal women, and it is associated with a better vaginal bleeding profile than CEE/MPA.¹⁶

Advantages: Subgroups of postmenopausal women with vasomotor symptoms in whom tibolone might have added value include women with sexual dysfunction, mood disorders, fibroids and urogenital complaints, as well as those with breast tenderness or high mammographic breast density with conventional HT use.

The other area where tibolone has an advantage is as add back therapy for the control of vasomotor symptoms associated with the use of GnRH analogues for the treatment of endometriosis and fibroids. In this situation, the increase in bone mineral density is also an added advantage.

Disadvantages: The main disadvantages with Tibolone are the reduction of HDL levels and weight gain.

Contraindications: These include pregnancy, undiagnosed vaginal bleeding, severe liver disorders, thromboembolic disease and some lipid abnormalities.

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