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Tibolone: Clinical recommendations and practical guidelines A report of the International Tibolone Consensus Group

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Abstract

An international multidisciplinary panel of experts in the management of the menopause met at the 4th Amsterdam Menopause Symposium in October 2004 to determine the specific place of tibolone, a synthetic steroid with a unique clinical profile, within the wide range of currently available postmenopausal therapy options. The consensus was that tibolone is a valuable treatment option for women with climacteric complaints.

As well as relieving vasomotor symptoms, tibolone has positive effects on sexual well-being and mood, and improves vaginal atrophy and urogenital symptoms. Prevention of bone loss with tibolone is comparable to that seen with estrogen therapy (ET) and estrogen/progestogen therapy (EPT). As tibolone rarely causes endometrial proliferation, no additional progestogen is required. It also has good tolerability, being associated with a low incidence of vaginal bleeding and of breast pain.

Tibolone does not increase mammographic density. Absolute numbers of women at increased risk for breast cancer are estimated to be low or absent with both tibolone and ET, and the risk with tibolone should be significantly lower than that with EPT. Tibolone might therefore be preferable to EPT in certain women who have not been hysterectomised.

Based on the evidence available, the panel proposed a number of subgroups of postmenopausal women with vasomotor symptoms in whom tibolone might have added value; these included women with sexual dysfunction, mood disorders, fibroids and urogenital complaints, as well as those with breast tenderness or high mammographic breast density with EPT use.

Keywords: Tibolone; Guidelines; Consensus statement; Recommendations; Mood; Sexuality; Breast density

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[1] The International Tibolone Consensus Group consisted of: M. Birkhäuser, N. Bundred, H. Burger, A.R. Genazzani, P. Kenemans (chair), L. Kiesel, A.O. Mueck, M. Neves e Castro, S. Palacios, L. Speroff (co-chair), J.C. Stevenson, M.J. van der Mooren, B. von Schoultz.
Note: ET is the abbreviation used to indicate postmenopausal hormone regimens that consists of unopposed estrogens only. Some members of the Group would have preferred the abbreviation ERT. Combined hormone use is indicated by EPT (some would prefer HRT).

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1. Introduction

An international multidisciplinary panel of experts in the management of the menopause met at the 4th Amsterdam Menopause Symposium (2–4 October 2004) to determine the specific place of tibolone within the current range of postmenopausal therapy options. Tibolone is a unique compound, widely used throughout the world for the treatment of climacteric symptoms. It has been registered in 90 countries for treatment of climacteric symptoms, and in 45 countries for the prevention of osteoporosis.

Tibolone has specific effects in different tissues due to tissue-selective metabolism, enzyme regulation and/or receptor binding and activation. After oral ingestion, tibolone is converted to three active metabolites: the 3α-OH and 3β-OH-tibolone metabolites have oestrogenic effects on the bone, vagina and climacteric symptoms, whilst the Δ^4 isomer has progestogenic and androgenic properties and prevents stimulation of the endometrium. The breast is also not stimulated due to effects on local enzyme activity that inhibit formation of active oestrogens. Tibolone has been classified as a selective tissue estrogenic activity regulator (STEAR) [1].

In the light of the results of the Women's Health Initiative (WHI) unopposed oestrogen therapy (ET) trial [2], and after the criticism [3,4] of the findings of the Million Women Study (MWS) [5], there is now room for reformulation of expert advice as to the use of postmenopausal hormone therapy. Several scientific societies e.g. EMAS and IMS, have recently updated their consensus statements and position papers [6,7]. These reports do not provide systematic practical guidelines and rarely mention tibolone. Because tibolone has a different profile to conventional ET, oestrogen–progestogen therapy (EPT) and selective oestrogen receptor modulators (SERMs), there is a need for separate guidelines that provide a practical tool for the gynaecologist and general practitioner in their everyday clinical practice.

There was a general consensus from the panel that tibolone is a valuable treatment option for women with climacteric complaints. In addition to improving climacteric symptoms, it has positive effects on sexual well-being and mood. It has good tolerability and is associated with a low incidence of vaginal bleeding and breast pain. With regard to breast cancer, the reassessment of recent data show that the absolute numbers of women at risk with ET and tibolone are low, if any, and that the risk with tibolone is lower than that with EPT. Tibolone might therefore, be preferable to EPT in women who have not been hysterectomised. It might also be preferable to ET in hysterectomised women who are more prone to sexual and mood problems.

2. The evidence

2.1. Efficacy

2.1.1. Climacteric symptoms

Randomised, placebo-controlled studies have confirmed that tibolone controls hot flushes, sweating and other typical symptoms such as insomnia, headache and fatigue. It has proved as effective as a range of EPT/ET regimens in relieving climacteric symptoms [8–10], although it may have a somewhat slower onset of action, and can be used as add-back therapy to relieve oestrogen-deficiency symptoms in women receiving gonadotrophin-releasing hormone (GnRH) agonist therapy for myomas or endometriosis [11,12].

- Consensus: tibolone is as effective as currently used EPT/ET regimens in the management of climacteric symptoms.

Level of evidence: proven

2.1.2. Urogenital symptoms

Tibolone has been shown to reverse vaginal atrophy (increases in karyopycnotic index and cell maturation value) and improve cervical mucus [13]. Women treated with tibolone have reported significantly less vaginal dryness, dyspareunia and urinary symptoms.

- Consensus: tibolone treats vaginal atrophy and relieves urogenital symptoms.

Level of evidence: proven

2.1.3. Libido and sexuality

The effects of tibolone on circulating androgens differ from those of standard oral hormone therapy

regimens. With tibolone, sex hormone binding globulin (SHBG) levels are decreased rather than increased, and therefore free testosterone levels are significantly increased as opposed to the decrease observed with standard EPT. Dehydroepiandrosterone sulphate (DHEAS) has also been shown to increase [14]. In addition, the Δ^4 isomer of tibolone has androgenic effects. These properties of tibolone contribute towards a beneficial effect on sexual well-being, including improvements in sexual desire, arousability, sexual fantasies and vaginal lubrication [15–17]. When compared with an EPT regimen, tibolone resulted in significantly greater improvement in coital frequency, enjoyment and satisfaction [18]. Similar significant improvements were reported with tibolone and a combination of oestrogen and androgen in terms of frequency of orgasm and sexual responsiveness, when compared with ET and controls [19].

- Consensus: tibolone has a positive effect on sexual well-being and is more beneficial than oral EPT/ET in this respect. However, no randomised controlled trials have been undertaken to specifically assess the effects of tibolone in female sexual dysfunction.

Level of evidence: potential
biologically plausible

2.1.4. Mood and depression

The significant beneficial effects of tibolone on mood are thought to be due to its normalisation of β-endorphin levels and its androgenic properties [15,20]. In a comparative study with EPT, tibolone proved more effective in improving mood disorders [21]. It may also act synergistically with psychoactive drugs, resulting in a faster improvement in women with depression or psychosis. As the use of antidepressant drugs is frequently associated with sexual dysfunction, the effects of tibolone on sexuality may have additional benefits in these women.

- Consensus: tibolone positively affects mood.

Level of evidence: expert opinion
biologically plausible

2.1.5. Quality of life

Beneficial effects on climacteric and urogenital symptoms, sleep, sexual drive and mood, combined with low rates of vaginal bleeding and breast tenderness, might be expected to result in an improvement in quality of life. A number of studies using specific quality of life and well-being scales have indicated that, in most women, significant improvements are seen with tibolone [9,22]. This has been confirmed during long-term everyday clinical experience with tibolone. Such experience-based evidence is important in assessing overall effects.

- Consensus: clinical experience with tibolone suggests that it improves quality of life.

Level of evidence: expert opinion

2.1.6. Prevention of bone loss

Randomised, controlled studies have shown that tibolone is effective in increasing bone mineral density (BMD) and preventing bone loss [23,24]. Beneficial effects are seen in both the femoral neck and spine. These beneficial effects are seen over long-term (10 years) treatment [25] and in both early and late postmenopausal women, women with established osteoporosis and women receiving GnRH agonist treatment [11,12,26–28].

- Consensus: tibolone is as effective as EPT/ET in preventing bone loss.

Level of evidence: proven

No data from randomised controlled trials on fracture risk are yet available.

2.2. Safety and tolerability

2.2.1. Breast tolerability

Tibolone causes significantly less breast tenderness and mastalgia than EPT and women are considerably less likely to stop taking tibolone than EPT for these reasons [8,9,23,29]. Women with EPT-induced breast tenderness or mastalgia appear to benefit from a switch to tibolone [30].

- Consensus: tibolone causes less breast tenderness and mastalgia than EPT.

Level of evidence: proven

2.2.2. Breast density

Tibolone does not increase mammographic density [29,31]. Naturally occurring increased mammographic density is considered to be an independent risk factor for breast cancer. Whether EPT-induced breast density is a surrogate marker for increased risk of breast cancer is currently unclear, however, increased mammographic density can mask breast tumours on screening mammograms thus causing delayed detection [32]. In addition, increased mammographic density results in an increased recall frequency that contributes to women's fear [33,34].

- Consensus: tibolone does not increase mammographic density.

Level of evidence: proven

2.2.3. Breast safety

As predicted from its mechanism of action, randomised controlled clinical trials have shown that tibolone has a different clinical effect on the breast to that of EPT. In contrast to EPT, tibolone does not increase breast tissue proliferation whilst stimulating apoptosis [31,35].

No increased risk of breast cancer has been observed compared with placebo in pooled data from all phase III/IV trials of tibolone (relative risk (RR) 0.50; 95% confidence interval 0.11–2.54) [36]. The MWS reported an increased RR of breast cancer with tibolone (RR 1.45; 95% confidence interval 1.25–1.67), although this was significantly ($p < 0.0001$) less than that seen with EPT [5]. Another epidemiological study using the UK General Practice Research Database (GPRD) showed no increased risk with tibolone (RR 1.02; 95% confidence interval 0.78–1.33) [37]. However, this study has been published only as an expended abstract, and not as yet as a full paper.

Although the best evidence currently available for the effect of tibolone on breast cancer is from the MWS, the risks reported in this observational study are probably overestimated [3,4]. Recent prospective trial data [2,33] show, that the absolute increase in risk for breast cancer is lower than reported in the MWS, and that the risks with tibolone and ET are probably lower than that with EPT.

- Consensus: randomised controlled trials investigating breast cancer incidence and tibolone are awaited before any firm conclusion can be drawn regarding tibolone and breast cancer.

Level of evidence: inconclusive

2.2.4. Endometrium

The selective local metabolism of tibolone into the Δ^4 metabolite, which has progestogenic properties, prevents endometrial proliferation and negates the requirement for the addition of a progestogen. The tissue-selective effect of tibolone on sulphatase also reduces oestrogenic activity in the endometrium.

Tibolone is associated with a low incidence of vaginal bleeding. Randomised controlled studies show that women given tibolone have significantly less irregular vaginal bleeding and a higher amenorrhoea rate than those given EPT [8,9,38].

Investigation of endometrial histology in women treated with tibolone shows no hyperplasia and a high level of atrophic endometrium [39,40]. No significant increase in endometrial thickness is seen when compared with women receiving EPT [38,41]. In contrast to EPT, tibolone does not increase the size or volume of myomas [42].

- Consensus: tibolone does not stimulate the endometrium and the addition of a progestogen is not required. It is associated with a high amenorrhoea rate and a lower incidence of irregular vaginal bleeding than continuous EPT. Standard endometrial surveillance is not required.

Level of evidence: proven

2.2.5. Cardiovascular

Clinical endpoint data from randomised controlled trials are currently not available for tibolone.

Some surrogate endpoints for arterial disease change in a favourable direction (triglycerides, lipoprotein(a), low-density lipoprotein cholesterol, particle size, endothelial function parameters, vascular tone), whereas others do not (high density lipoprotein cholesterol, C-reactive protein) [43].

Either potentially favourable effects or no changes are seen in some risk markers for venous thromboembolic disease (APC resistance, anti-thrombin, protein C, fibrinogen, factor VII, plasminogen, PAI-1, PAP complex, TDP), whereas other markers (F1 + 2, TAT, D-dimer) show procoagulatory changes [44].

- Consensus: cardiovascular clinical outcomes from randomised controlled trials are not available yet. Surrogate endpoint studies for arterial disease and venous thromboembolic disease are inconclusive with regard to benefit or risk.

Level of evidence: inconclusive

2.2.6. Overall tolerability

Tibolone has proven tolerability. The most common adverse events are leukorrhoea, abdominal pain, weight increase, vaginal bleeding and breast pain. However, vaginal bleeding and breast pain are significantly less common with tibolone than with continuous EPT. When compared with pre-treatment values in a study of more than 1000 women, tibolone use resulted in a significant reduction in a wide range of complaints including weight gain [45]. Studies have shown that tibolone prevents the increase in body fat mass and the decrease in lean body mass that typically occur in postmenopausal women [46,47].

- Consensus: tibolone is well tolerated. It has no major clinical impact on body weight.

Level of evidence: proven

3. Guidelines

The consensus of the panel was that tibolone is a valuable treatment option for women with climacteric complaints. In addition to improving climacteric symptoms, it has a mostly positive effect on sexual well-being and mood. It has good tolerability and is associated with a low incidence of vaginal bleeding and breast pain. With regard to breast cancer, the recent data show that the absolute numbers of women at risk are low. The risk with tibolone is comparable to that with ET and is probably lower than that with EPT. The WHI study indicated no increased risk of breast cancer with ET alone [2]. Whereas ET can be considered as a safe treatment option for women without a uterus, tibolone might be preferable to EPT in women who have not been hysterectomised. It might also be preferable to ET in hysterectomised women who are more prone to sexual and mood problems.

Based on the available evidence, the panel proposed the following:

3.1. Postmenopausal women with vasomotor symptoms in whom tibolone might have added value

- Women with low sex drive, or so-called female sexual dysfunction.
- Women with mood disorders or those receiving psychoactive treatments.
- Women at risk of accelerated bone loss.
- Women with premenopausal breast tenderness or mastalgia.
- Women with high breast density.
- Women with fibroids.
- Women with urogenital complaints.

3.2. Women who might benefit from a switch from EPT/ET to tibolone

The panel suggested that some groups of women might benefit from a change to tibolone from conventional EPT/ET:

- Women with increase in breast pain or mastalgia.
- Women with an increase in breast density causing false recalls or unreadable mammograms.
- Women with low sex drive.
- Women with mood disorders.
- Women with bleeding problems (providing no histopathological reasons exist for bleeding).

3.3. Women without climacteric symptoms to consider

The panel also suggested that some postmenopausal women without climacteric symptoms, or with only mild symptoms, might benefit from tibolone treatment:

- Women with low sex drive.
- Women with mood disorders.
- Women with osteopenia.

3.4. Other groups of women to consider

In addition to postmenopausal women with a natural menopause, the panel also considered the use of tibolone in younger women:

- Women with premature menopause – no consensus was reached about the use of EPT, ET or tibolone. Several members agreed they would use tibolone in this indication, particularly if the women were suffering from mood and sexual problems, whilst others preferred to use EPT/ET.
- Women receiving long-term add-back GnRH agonists for endometriosis – the panel agreed that tibolone may be beneficial in relieving oestrogen deficiency symptoms and preventing bone loss in these women.

3.5. Contraindications to tibolone

The panel recommended that the contraindications to tibolone should be considered to be the same as for EPT/ET.

4. Concluding remarks

This consensus on the clinical recommendations and practical guidelines for the use of tibolone in postmenopausal women has been formulated by experts with experience in the field of postmenopausal hormone therapy and tibolone use, on the basis of the best available evidence.

As indicated, the best available evidence is not always identical with the desired "Level I" evidence obtained with prospective randomised controlled trials. However, it was felt that where these optimal data were lacking, the statement that "further research is needed" would not really provide a practical tool for the gynaecologist and general practitioner for their every day clinical use.

The expert group has tried to put the available evidence together in a practical document. However, each decision in medical practice should be patient tailored, taken after proper counselling, by the patient and the doctor together, based on individual knowledge and personal expertise.

Declaration of interest

Several authors have been sponsored by pharmaceutical companies to speak publicly about postmenopausal hormone therapy, both for and against. Several authors have received research and/or educational grants from pharmaceutical companies (which do and do not have hormone therapy products) and from non-commercial sources, research councils and charities to conduct research in the field of menopause and postmenopausal hormone therapy.

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