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GENERAL GYNECOLOGY: REVIEW

Tibolone and Breast Tissue: a Review

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Abstract
The safety profile of hormone replacement therapy (HRT) on breast is still controversial. Tibolone is an option of treatment for climacteric syndrome of postmenopausal women. Its risk profile on breast is debated. This is an updated narrative review focusing on the impact of tibolone on breast. Particularly, we will report data from major preclinical and clinical studies regarding the effects of the use of this compound on breast tissue and breast density. Moreover, we will analyze and discuss the most relevant findings of the principal studies evaluating the relationship between tibolone and breast cancer risk. Our purpose is making all clinicians who are particularly involved in women's health more aware of the effects of this compound on breast and, thus, more experienced in the management of menopausal symptoms with this drug. According to the available literature, tibolone seems to be characterized by an interesting safety profile on breast tissue.

Keywords Tibolone · Breast · Menopause · Hormone replacement therapy · Breast density · Breast cancer

Introduction

After the publication of Women's Health Initiative (WHI) study [1], many women stopped and/or refused menopausal hormone therapy (MHT), giving up the benefits associated with this treatment in terms of quality of life and prevention of osteoporosis and/or some chronic diseases [2]. Breast cancer (BC) risk under MHT is a clinically relevant issue, not only for physicians but also for patients, who often avoid taking MHT because of the fear of this tumor. However, it should be taken into account that different types of MHT may be associated with different relative risks of BC, since MHTs include several formulations that can differ from each other. In particular, tibolone is characterized by a unique pharmacological and clinical profile [3].

This is a narrative review focusing on the effects of tibolone on breast; in particular, we review preclinical data, effects on mammographic density and on BC risk in postmenopausal women.

Materials and Methods

This is a narrative review regarding the general impact of tibolone on breast, including the most relevant data until May 2022.

More precisely, a systematic search of PubMed and Medline databases was conducted by using the keywords "tibolone," "breast," "breast density," "breast cancer," and "breast tissue."

The following inclusion criteria were applied:

- International studies, mostly published in the last two decades.
- Study types: "clinical trial," "randomized controlled trial," "meta-analysis," "systematic review," "practice guidelines," "guideline," "review."
- Publications in English language.

Our review excluded papers published in non-peer-reviewed journals and/or supplements.

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Preclinical Studies

According to preclinical data, tibolone can inhibit DMBA (7,12-dimethylbenz[a]anthracene)-induced mammary tumor in rats [4].

Moreover, tibolone can inhibit proliferation and stimulate apoptosis of normal and transformed breast epithelial cells [5]. Besides, tibolone inhibits sulphatase activity, significantly decreasing the intra-mammary formation of active estrogenic compounds [6] and, thus, reducing the formation of free estrone from estrone sulphate.

Effects of Tibolone on Normal Breast Cells and Breast Cancer Cells

In normal breast cells, tibolone and its delta4-isomer significantly increase apoptosis, as demonstrated by flow cytometry and morphological studies [7]. These effects are due to the ability of tibolone and its metabolite delta4-isomer to interfere with the activity of 17beta-hydroxysteroid-dehydrogenase type 1 and to inhibit the expression of the anti-apoptotic protein Bcl-2 in normal breast tissue [8].

In hormone-dependent BC cells, tibolone and its metabolites seem to inhibit significantly the conversion of estrone sulphate into estradiol through a negative modulation of breast enzymes that locally produce active forms of estrogens [9–11].

According to Cline et al. [12], in a model of ovariectomized cynomolgus monkeys, after 2 years of treatment with tibolone, breast tissue did not undergo significant stimulation in comparison with conjugated equine estrogens (CEE) alone or CEE plus medroxyprogesterone acetate (MPA). Conversely, CEE and CEE + MPA seemed to promote an increase of breast epithelial tissue area and an augmented expression of Ki67.

In a DMBA-rat model, tibolone inhibited tumor growth and initiation similarly to tamoxifen [11].

Moreover, in nude mice, tibolone did not stimulate normal breast cells, as demonstrated by the evaluation of estrogenic activity markers [3], and it did not stimulate MCF-7 cells transplanted in the same experimental model [13].

Clinical Studies

Tibolone Does Not Stimulate Breast Tissue: the (Potential) Biological Reasons

Shortly, after the introduction of tibolone in the management of menopausal symptoms, women treated with this compound seemed to be characterized by weaker breast tenderness and lower mammographic density in comparison with those occurring during estrogenic-progestogen therapy [14].

Actually, tibolone seems to exert a reduction of estrogenic activity on breast tissue and a tumor-inhibiting effect through different putative mechanisms (Fig. 1).

Firstly, transactivation studies ruled out an antagonistic effect on steroid receptors [15]. Secondly, the sulphated 3alpha-OH tibolone metabolite can produce an irreversible inhibition of sulphatase. Thirdly, 17beta-hydroxysteroid dehydrogenase activity was slightly inhibited whereas sulfotransferase activity was stimulated at low concentrations. As a result, a predominance of sulphated forms from endogenous estrogens and estrogenic-metabolites of tibolone — that are virtually inactive regarding mitotic activity — could be detected.

Tibolone and Breast Density

It is recognized that the radiological breast parenchymal pattern may be a marker of BC risk [16].

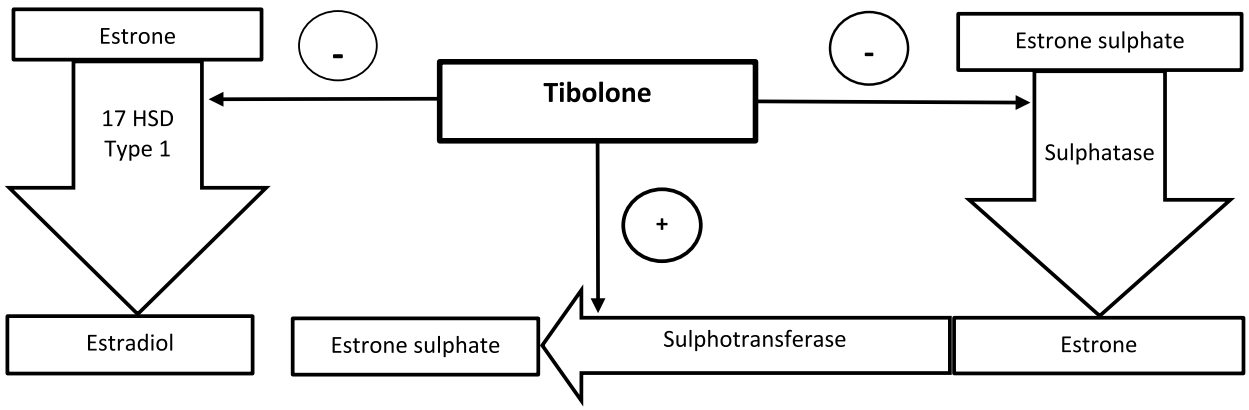

Fig. 1 Tibolone: enzymatic regulation within breast

In fact, although the relationship between histological features and mammographic breast density (BD) remains unclear, it has been suggested that BD may reflect the proliferation of breast epithelium and stroma [17]. Therefore, an increased BD is thought to be per se a risk factor for BC, and, thus, it has been incorporated into some predictive models [18, 19].

On the other hand, increased MBD may be considered one of the possible potentially undesired and dangerous side effects of MHT. Women with increased BD under MHT often face breast tenderness and pain, which can reduce the adherence to this treatment [20]. A study by Leung et al. [21] on 306 postmenopausal women (mean age > 54 years) compared mammograms of 148 MHT users with those of 158 non-users. The authors found a significant increase of mean density score in MHT users vs non-users (4.7 versus 3.4; $p < 0.001$); this difference was confirmed after further stratification, and density score was not affected by the duration of MHT use (> or < 5 years).

Interestingly, BD under MHT is a changing parameter, which can show an increase or a decrease, after the start and the discontinuation of therapy, respectively [22].

Unfortunately, augmented BD can decrease mammographic sensitivity [23], and can compromise breast screening by impairing the interpretation of mammograms [24, 25]. Women with increased BD on mammographic evaluation during MHT need to repeat mammographic examination 1 month after the interruption of treatment to avoid reducing mammographic sensitivity [26].

Clinically, higher BD without MHT depends on the impact of endogenous hormones on breast tissue and, as aforementioned, maybe a surrogate marker of increased BC risk. However, increased BD detected under MHT may result from the action of exogenous hormones on breast.

In 1998, Erel et al. [27] studied 25 postmenopausal women using high-resolution mammography. After 24 months of tibolone therapy (2.5 mg/day), only one patient out of 25 had an increase of BD (by 10%), while the remaining women did not. No patients reported breast discomfort during the 24-month period of observation.

A study by Özdemir et al. [28] on 118 postmenopausal women, 88 under MHT and 30 controls (median follow-up of 16.92 ± 7.65 months), found that the increase of BD reported with tibolone was 18%, whereas those obtained with other therapies appeared higher (estrogen + cyproterone acetate: 46%; estrogen + MPA: 43%; estrogen alone: 28%).

Interestingly, Valdivia and Ortega studied the effect of different MHTs on BD after 12 months of therapy [29]. Participants were randomly assigned to one of the following treatments: (a) estradiol (E2) 2 mg; (b) E2 2 mg + sequential MPA 5 mg; (c) E2 2 mg + continuous MPA 2.5 mg; (d) CEE 0.625 mg; (e) CEE 0.625 mg + sequential MPA 5 mg; (f) estriol 2 mg; (g) tibolone 2.5 mg; 30 age-matched untreated subjects served as control group. Mammograms were evaluated by two independent radiologists in a double-blind manner, according to Wolfe classification [16, 30] identifying four categories: N1: normal breast tissue (mostly fat tissue and little fibrous connective tissue in the parenchyma, no ducts visible; this pattern was associated with the lowest risk of BC); P1: condition of parenchyma fat, ductal pattern equal or more than one-fourth of the breast gland (low risk of BC); P2: prominent ductal pattern more than one-fourth of the breast gland (high risk of BC); DY: very dense parenchyma (probably indicating hyperplasia of connective tissue) related to the highest risk of BC. Before the start of the study, 81% of mammograms were rated as N1 or P1. The percentage of subjects with an increase of mammographic density was significantly greater in MHT users than controls: 31.9% (95% confidence interval (CI): 25.7–38.6%; 67 of 210 MHT users) vs 3.3% (95% CI: 0–17.2%; 1 of 30 controls). An increase of BD was reported for groups (a) to (e), while no patients treated with tibolone or estriol had a significant increase of BD ($p < 0.05$ in comparison with all MHT-treated groups).

Tibolone 2.5 mg/die ($n = 24$) was compared with other types of MHTs in a 1-year prospective study [31] on 121 postmenopausal women treated with continuous transdermal 17beta-estradiol (TDE2) 50 mcg/die plus sequential nomegestrol acetate (NomAc) 5 mg/die for 12 days/month ($n = 26$), continuous TDE2 50 mcg/die plus NomAc 2.5 mg/die ($n = 25$), and continuous TDE2 50 mcg/die ($n = 23$). Twenty-three women who did not receive any treatment served as control group. After 12 months of MHT, increased mammographic density was reported in 35% of women treated with TDE2+NomAc in sequential manner, 42.85% of women on continuous combined TDE2+NomAc, 21% of subjects on continuous TDE2, and 10% of tibolone group. No variation of BD was observed in controls. The increase in BD reported for continuous sequential TDE2/NomAc, continuous combined TDE2/NomAc, and continuous TDE2 was statistically significant ($p < 0.05$) in comparison to tibolone group; interestingly, no statistically significant difference between tibolone group and control group was observed ($p = 0.49$). Thus, according to the latter study, tibolone did not significantly change BD [31].

In a study by Lundström et al. [32] on a total of 154 women, tibolone ($n = 51$) was compared to placebo ($N = 55$) and a continuous combined MHT ($N = 48$) containing estradiol 2 mg/norethisterone acetate 1 mg (E2/NETA) regarding the changes of BD. Breast density was assessed at baseline and after 6 months of therapy through the evaluation of the area with a dense pattern of the breast (expressed as percentage) and the Wolfe classification [16, 30].

The mammograms were analyzed by two independent radiologists blinded to treatments. A significant percentage

of increase of BD was reported in the group treated with E2/NETA in comparison with tibolone group (46–50% versus 2–6%; p for difference: <0.001), while no difference between tibolone and placebo was reported. The relative risk (RR) of an increase of BD was higher for E2/NETA compared with tibolone (RR = 8.3; 95% CI: 2.7–25.0).

Breast pain was significantly less often reported in tibolone group ($n = 2$; 4%) than in the E2/NETA group ($n = 18$; 33%, $p < 0.001$ for difference); no breast pain was reported by controls. Thus, tibolone seemed to induce only a modest stimulation of breast tissue in comparison to estrogen/progestogen treatment.

Another, open-label, non-randomized study evaluated the long-term effect of tibolone on BD [33] in postmenopausal women. Mammography was performed during visits at baseline, 1, 6, 8, and 10 years, in 32 women treated with tibolone and in 28 controls; mammograms were retrospectively reviewed by two independent radiologists, blinded to the treatment, using Wolfe classification for grading. There were no statistically significant differences between tibolone and control group regarding BD at baseline and after 10 years. This study seemed to suggest that tibolone did not increase BD, neither in the long-term administration. Hence, even a long-term use of tibolone could not hamper the analysis of mammograms by radiologists.

Tibolone and Breast Cancer

In 2003, the Million Women Study (MWS) [34], a large study conducted in the United Kingdom (UK) on 1,084,110 women aged 50–64 years invited for BC screening, concluded that the treatment with tibolone was associated with increased BC risk, with a RR = 1.45 (95% CI: 1.25–1.68, $p < 0.0001$), similar to that associated with estrogen therapy [1.3 (95% CI: 1.21–1.40], $p < 0.0001$], but significantly less than that observed for continuous combined HT [2.0 (95% CI: 1.88–2.12), $p < 0.0001$]. However, afterwards, some criticisms regarding MWS emerged [35]. Firstly, MWS was an observational study, based on information provided by the participants. Secondly, it is plausible that a sort of so-called preferential prescribing by physicians towards patients with a higher risk of BC occurred. In other words, in UK, physicians seemed to prescribe tibolone preferentially to women with increased risk of breast and endometrial cancer as compared with women to whom were prescribed estrogen + progestogen products.

Moreover, women who attended for routine mammography maybe not representative of the general population. MHT users and/or women with known breast lumps could be more probably enrolled in the study because of the need of monitoring therapy to exclude BC risk. In addition, that analysis failed to record discontinuation of MHT use or crossovers, without an adequate classification of the starting time, type, and duration of therapy. Overall, all these points are crucial to properly assess the effective BC risk. Furthermore, women enrolled in the MWS were part of a non-homogeneous group; indeed, women on MHT were more numerous than those who refused to take part to this study (32 versus 19%), and resulted with greater rate of BC than the general population (2.8 versus 2.0 per 1000). Actually, all these conditions can give a selection bias. Furthermore, the data on MHT use were extrapolated from interviews and were subjected to recall bias since participants were aware of the study's aim [36, 37].

In 2003, another population-based case–control study conducted in UK by Opatrny et al. [38] was performed to determine the effect of different types of MHT on the risk of BC in postmenopausal women (50–75 years old) selected from GPRD (General Practice Research Database). More specifically, 6347 incident cases of BC were matched with 31,516 controls. The rate of BC was not increased among users of unopposed estrogens (RR 0.97; 95% CI 0.86–1.09) or tibolone (RR 0.86; 95% CI 0.65–1.13). However, tibolone users who switched from opposed estrogens had an elevated rate of BC risk (RR 1.29; 95% CI 1.09–1.52).

The use of oral combined estrogen-progestin therapy was associated with a higher risk of BC that increases with use. Thus, according to this study, both unopposed estrogen and tibolone did not increase BC risk. Clearly, these results for tibolone were in conflict with those of MWS.

A multinational, multi-center, randomized, double blind, parallel group, placebo-controlled trial, the LIBERATE trial (Livial Intervention following Breast Cancer: Efficacy, Recurrence, And Tolerability Endpoints) [39], aimed to show the non-inferiority of tibolone versus placebo regarding the risk of recurrence of BC in postmenopausal BC patients with climacteric complaints. Women surgically treated for a histologically confirmed BC affected by vasomotor symptoms were randomly assigned to either tibolone 2.5 mg daily ($n = 1556$; man age: 52.5 years) or placebo ($n = 1542$; man age: 52.9 years). The hazard ratio (HR) for tibolone versus placebo after 3.1 years was 1.397 (1.144–1.704; $p < 0.001$). These findings could be explained by the fact that the effect of tibolone on BC cells may be quite different from its activity on normal breast cells: in other words, the ability of this compound to reduce estrogenic stimulation of breast tissue through the modulation of sulphatase and sulfotransferase may be not preserved in BC tissue. Thus, this study demonstrated that tibolone cannot be used in women with past or suspected BC, due to the increased risk of recurrence [39].

Interestingly, a Cochrane review published in 2016 [40], based on four RCTs (overall, 5.500 women), did not report significant differences regarding BC incidence between groups (treated with tibolone vs non-treated) among women without a history of BC (OR 0.52, 95% CI 0.21 to 1.25),

while it confirmed an increased risk of BC recurrence associated with tibolone use among women with previous BC (OR 1.5, 95% CI 1.21 to 1.85; two RCTs; 3165 women).

A meta-analysis published in 2019 [41] provided data about the effects of exposure to MHT and BC risk for the most commonly prescribed MHT types from 24 prospective observational studies. In this meta-analysis, the risk of BC resulted higher for estrogens only, estrogen-progestogen, and tibolone current users; moreover, the results showed a remaining increased risk even after discontinuation of MHT. However, the included studies were conducted in different settings, based on different selection criteria, and considering different definitions of exposure; thus, methods and original study designs were heterogeneous.

Additionally, this important meta-analysis was based on observational studies; thus, it is not possible to completely exclude biases as well as confounding effects, as also reported in a comment by The International Menopause Society [42].

In 2020, Vinogradova et al. [43], in a study based on two nested case–control studies (n = 98,611 women aged 50–79 with a primary diagnosis of BC matched to 457498 controls), did not report an increased BC risk from short-term use of tibolone; moreover, the increasing duration of MHT use was generally associated with increased BC risk, but tibolone (as well as estradiol-dydrogesterone) resulted to be linked to the smallest risks. Finally, 2 years after the discontinuation of tibolone, no significantly increased BC risk was reported.

Recently, a nested case–control study based on data insurance in South Korea from 36,446 women using or having used MHT for more than 1 year and in 36,446 women who did not use any MHT for more than 1 year investigated the relationship between the type and duration of MHT and BC incidence [44]. In this study, BC risk was reported to be decreased with tibolone use for all ages of subjects. In particular, BC risk was lower with tibolone in women staring therapy aged ≥50 years, thus, at early stage of menopause. Menopausal hormone therapy use for <3 years was associated with lower BC risk with tibolone, while higher risk was observed with estrogen-only therapy.

Discussion and Conclusions

Menopausal hormone therapy is a first-line therapy to treat climacteric syndrome, improving quality of life, and preventing some chronic conditions of postmenopausal women (e.g., osteoporosis) [2]. The availability of different effective and safe treatments can favor the adherence of patients.

Tibolone is a pro-drug that, after oral ingestion, is metabolized into three main compounds, two with estrogenic activity (3alpha-hydroxy-tibolone and 3beta-hydroxy-tibolone) and one with androgenic and progestin activities (delta4-isomer) [4, 11].

In the breast tissue, tibolone and its metabolites can inhibit sulphatase activity (that catalyzes the transformation of estrone sulphate into estrone, which in turn can be metabolized into estradiol, with possible, subsequent increased cellular proliferation) and increase the sulphotrasferase activity (that catalyzes the production of estrone sulphate from estrone) (Fig. 1). These actions decrease the production of active estrogens within breast of postmenopausal women treated with this compound [14].

Therefore, given its pharmacological mechanism of action, tibolone does not significantly increase breast stimulation and BD, even after long duration of administration [26]. Overall, tibolone does not appear to increase the relative risk of developing BC.

Considering its beneficial effects on hot flushes and sweating, sexual function, vulvo-vaginal atrophy (VVA), and quality of life, many years after its introduction in clinical use, tibolone still remains a possible treatment of first choice in the management of postmenopausal women, due to its efficacy and safety.

Author Contribution The authors contributed equally to this article.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors. The study was a literature review; thus, it did not require the approval of a specific Institutional Review Board and Ethics Committee.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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