Treatment of VVA – hidden interests?

Vulvovaginal atrophy (VVA) is a major consequence of menopause and related loss of the estrogenic effect on the vaginal epithelium. For many decades, the ideal therapeutic approach was to use systemic estrogen, which was very effective. Local treatment with vaginal estrogen (creams, tablets, and rings) is effective to the same extent. But, on the other hand, the downside of systemic hormone therapy (risks for breast cancer, cardiovascular and thromboembolic events, perhaps some cognitive decline) became a major issue after the first release of data from the Women's Health Initiative (WHI) trial in 2002, and changed both patients' preferences and prescription habits. The uncertainty about estrogen resulted in two changes concerning the treatment of VVA. The first has been to lower the dosage of local estrogen preparations, still maintaining a good clinical response and symptom relief, but keeping serum estrogen levels well below premenopausal levels. The other was to promote non-estrogenic and non-hormonal therapies, either by using marketed products, or by developing new drug formulations. Among the recently approved medications is prasterone – an intravaginal DHEA preparation [1,2]. In a 52-week-long study which showed a significant improvement in vaginal dryness and irritation/itching, and in pain during sexual activity, the authors commented that 'The treatments currently used against VVA are essentially intravaginal and oral estrogen; however, as indicated by the black box on the estrogen information leaflets, there are risks. In fact, even at the lowest dose and dosing regimen, all intravaginal estrogen preparations increase serum estrogens above the normal postmenopausal range or above the threshold of no biological activity with the accompanying risk of systemic effects' [2]. Is this statement supported by hard clinical data?

Comment

Many menopause and ObGyn societies have produced guidelines/recommendations/position statements on the management of VVA. The 2013 North American Menopause Society position statement said 'Vaginal estrogen is inappropriate for postmenopausal women with undiagnosed vaginal/uterine bleeding and controversial in women with estrogen-dependent neoplasia (e.g. breast, endometrial)' [3]. Earlier recommendations by the International Menopause Society (IMS) said that 'Local vaginal estrogen therapy is preferable when systemic treatment is not needed for other reasons, because local therapy avoids most systemic adverse events and is probably also more efficacious for vaginal problems' [4]. Based on the good safety profile of topical estrogen, the commercial interest to develop and market alternative therapies seems intriguing and needs to be clarified. According to the IMS recommendations, there is no evidence of any increase in thromboembolic events or increase in metastases in breast cancer survivors who were using vaginal estrogen tablets for symptom relief [4]. As for the endometrium, studies did not record cases with hyperplasia or carcinoma, but the duration of follow-up was relatively short and long-term data (> 1 year) are lacking. Thus the available clinical database favors the use of local estrogen in almost all women. So why did the industry invest so much money in developing new medications, which are expected to capture only a relatively small market share?

The answer lies in the aftermath of the WHI study. The anti-estrogen publicity in the media led to abandonment of all sorts of hormone therapy because of fears of severe untoward reactions. Needless to say that the sales of all non-estrogenic preparations also receive a boost from media reports which are based on the current contents of the patient information leaflets of vaginal estrogen. Basically, all have black-box warnings accompanied by textual clarification. Here are two representative examples: the leaflet accompanying Vagifem ® states: 'In the absence of comparable data, these risks should be assumed to be similar for conjugated estrogen or other dosage forms of estrogens' [5]; the Premarin cream® leaflet states: 'Systemic absorption occurs with the use of Premarin vaginal cream. The warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account' [6]. As quoted in the first paragraph of this

commentary, the scientific articles that bring new clinical data on the non-estrogenic treatment modalities always stress the alleged problematic safety profile of vaginal estrogen [2].

Since the official prescribing information of local estrogenic products and its black-box warnings may not reflect the body of the relevant medical literature, there is no wonder that a group of key opinion leaders in the USA decided to appeal to the FDA authorities with a request to change the labels and delete the black-box warnings [7]. The group states that 'The boxed warning, which reflects estrogen class labeling, is based on extrapolations of data from clinical trials of systemic hormone therapy such as the WHI, which involved substantially higher levels of exposure. We believe that the boxed warning is not evidence-based and harms women by discouraging the use of a highly effective local treatment of a common condition.' As for the three main safety concerns, phrasing is very cautious, yet unbiased: 'Women with a history of cancer of the breast or uterus … are encouraged to consult their oncologist before using this product; low-dose vaginal estrogen therapy does not seem to have significant endometrial impact beyond the local vaginal estrogenic effects; the increased risks of coronary heart disease, stroke, and VTE, which have been reported with oral systemic hormone therapy, have not been reported with low-dose vaginal estrogen therapy.'

In conclusion, therapeutic alternatives are always welcomed, and competition is usually beneficial for the consumers. However, the flow of information on the newer products indicated for VVA seems to include an inaccurate message, which downgrades the use of estrogenic preparations and upgrades modern non-estrogenic therapies. We should focus on comparing the efficacy and benefits of the various drugs rather than promoting safety issues which are not substantiated by hard clinical facts.

Amos Pines

Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

and

David Sturdee

Solihull Hospital, Birmingham, UK

References

1. Archer DF. Dehydroepiandrosterone intra vaginal administration for the management of postmenopausal vulvovaginal atrophy. J Steroid Biochem Mol Biol 2015;145:139-43 http://www.ncbi.nlm.nih.gov/pubmed/25201455
2. Archer DF, Labrie F, Bouchard C, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause 2015 Mar 2. Epub ahead of print http://www.ncbi.nlm.nih.gov/pubmed/25734980
3. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 2013;20:888-902 http://www.ncbi.nlm.nih.gov/pubmed/23985562
4. Sturdee DW, Panay N; International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010;13:509-22 http://www.ncbi.nlm.nih.gov/pubmed/20883118

http://www.novo-pi.com/vagifem.pdf

http://labeling.pfizer.com/showlabeling.aspx?id=132

- Manson JE, Goldstein SR, Kagan R, et al. for the Working Group on Womens Health and Well-Being in Menopause. Why the product labeling for low-dose vaginal estrogen should be changed. Menopause 2014;21:911-16 http://www.ncbi.nlm.nih.gov/pubmed/25140698