Women & Health

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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/wwah20

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To cite this article: Márcio Alexandre Hipólito Rodrigues & Márcia Mendonça Carneiro (2022) Estrogen in female health: friend or foe?, Women & Health, 62:2, 95-97, DOI: 10.1080/03630242.2022.2035484

To link to this article: https://doi.org/10.1080/03630242.2022.2035484

Published online: 07 Feb 2022.

WOMEN & HEALTH
2022, VOL. 62, NO. 2, 95–97
https://doi.org/10.1080/03630242.2022.2035484

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EDITORIAL

Estrogen in female health: friend or foe?

The importance of estrogen for women goes way beyond their action in the reproductive axis but spreads over various body functions from cardiovascular function and bone health to brain functions and cognition. Recent findings linking hypoestrogenism after bilateral oophorectomy before menopause accelerated aging and morbidity corroborating the vital role estrogen plays in female health (Rocca et al. 2021). Estrogen may also interact with the gut microbiome and result in a variety of estrogen-mediated effects in female health and disease ranging from obesity, metabolic syndrome, infertility, endometriosis, and cancer (Baker, Al-Nakkash, and Herbst-Kralovetz 2017).

Moreover, we cannot refrain from mentioning that the reduction in estrogen production in natural menopause results in a series of symptoms, such as hot flashes, vaginal dryness, and dyspareunia, in addition to the acceleration of the atherosclerotic process and increased cardiovascular risk. However, the use of estrogens in conditions where there is a gradual or sudden reduction in their plasma concentration still remains controversial not only for the scientific community, but for health-care providers involved in the care of these women. Specifically, the use of estrogens during the peri- and post-menopausal period went through a discredit phase after the results of the main randomized placebo-control study, the Women's Health Initiative (WHI) (Rossouw et al. 2002).

The identification of estrone (E3) and estradiol (E2) by Edward Doisy (Simpson and Santen 2015) more than 80 years ago unveiled new horizons for the use of estrogenic compounds during a woman's reprodutive life ranging from contraception to the relief of vasomotor and urogenital symptoms during the peri- and post-menopausal period. Later, in the 1980s, another major breaktrough was the purification of human aromatase cytochrome P450, a key enzyme that converts androgens (androstenedione) to estrogens (estrone) (Simpson and Santen 2015) which opened up a new era in the treatment of breast cancer with the development of aromatase inhibitors (AI).

Despite such advancements, the role of estrogen in female health remains a matter of debate. The management of estrogen-related complaints raises questions related to the safety and possible adverse effects regarding its role in breast and endometrial cancer for example as well as its thrombogenic activity. Thus, treating the symptoms of hypoestrogenism in women undergoing breast cancer treatment remains a challenge as estrogen is formally contraindicated in this setting.

Recently, the possible role of estrogen in cognitive function of post-menopausal women undergoing treatment for breast cancer with AI shows cognitive decline with deterioration in working memory and concentration 12 to 18 months after initiation of therapy (Bender et al. 2015). Hope lies in the development of compounds such as selective estrogen receptor modulators (SERMS), with tissue-dependent agonistic, antagonistic, or a combination of both actions. One of these SERMS, tamoxifen which has antiestrogen action in the breast, provides an agonist action in bone, preserving bone mineral density and thus represents an option in osteoporosis prevention which is also a major health issue for postmenopausal women (Pickar, MacNeil, and Ohleth 2010). Thus, none of the currently available SERMS has managed to broaden the spectrum of positive actions, especially with regard to the bothersome vasomotor symptoms that arise during this kind of therapy.

After the publication of the ominous results of the WHI, menopause hormone therapy prescription fell heavily and women were left with no option but bear the burden of hypoestrogenism or face the risks of breast cancer and thrombosis. Fortunately, years after the WHI, the results were re-evalauted and many questions raised regarding the interpretation and clinical application of such data. It was time to open our minds to new directions in favor of a rational use of MHT which considered the

"timing hypothesis" (Clarkson 2007; Hodis et al. 2016). Women in the WHI were much older than the natural age at menopause which could mean they were beyond the "window of opportuity" to benefit from estrogen replacement.

In the meantime, a new and interesting concept has emerged, "*eu-estrogenemia*" (Turner and Kerber 2017). The authors carried out an extensive analysis to demonstrate that the discrepant results between observational and randomized studies, and the "*window of opportunity*" theory (Hodis and Mack 2013a, 2013b) could be closely linked to the *eu-estrogenemia* theory; so, in situations where estrogen levels would be low, a worsening of cardiovascular function would be present (Turner and Kerber 2017). These authors argued that this concept could be applied also in situations where estrogens demonstrated a neuroprotective effect, as estrogen-therapy was able to protect the brain tissue of oophorectomized mice through anti-inflammatory actions and, in turn, reinforcing the concept that maintaining estrogen blood levels would prevent the harmful effects of hypoestrogenism in the central nervous system (Suzuki et al. 2007).

Although described in 1960 by Diczfalusy, estetrol (E4), an estrogenic steroid molecule synthesized exclusively by the fetal liver during human pregnancy (Coelingh Bennink, Holinka, and Diczfalusy 2008), gained attention almost 40 years later due to its pharmacological profile with either agonist or antagonist action, depending on the target organ. This new estrogen molecule is considered a natural human fetal SERM, and its clinical effects occur through estrogen receptors and with preference for ER-α. Available experimental data have shown that the E4 behaves as an agonist in tissues like bone, vagina, endometrium, and brain, and may be an useful drug for osteoporosis prevention and the alleviation of vasomotor and urogenital symptoms. In addition, E4 effectively inhibits ovulation with slow liver metabolism, no stimulation of SHBG synthesis, and no inhibition of cytochrome P450 in addition to being 10 to 20 times less potent than ethinylestradiol (EE) which may suggest a potential low risk of venous thromboembolism when used in humans. Conversely, E4 shows antagonistic action on breast tumor tissue (Coelingh Bennink, Holinka, and Diczfalusy 2008).

Recently, a randomized, open-label, controlled, 3-arm, parallel study demonstrated that combining E4 15 mg with drospirenone 3 mg resulted in a combined oral contraceptive (COC) with a different metabolic profile in comparison to EE-containing products (Klipping et al. 2021). Studies analyzing the efficacy and safety of the use of E4 in postmenopausal women are still in the recruitment phase, but a multicenter, randomized, double-blind, placebo-controlled study by Gaspard et al. (2020) shows that E4 15 mg is considered to be the minimum effective daily oral dose for treatment of vasomotor symptoms. Although no cases of hyperplasia were detected despite increased endometrial thickness, the authors warn that this is further to be confirmed in phase 3 clinical development.

In summary, estrogen is pivotal hormone for female health as it orchestrates a variety of vital functions that may shift the balance from health to disease. Similarly to Dr Jekyll and Mr Hyde, estrogen may show its good or an evil face depending on the circumstances. Since its identification more than 80 years ago, much has been unraveled but a great deal remains to be ellucidated. It is clear, however, that women do suffer when deprived of estrogen but it can easily promote disease once favorable conditions arise. Therefore, the research agenda should include not only studies on estrogen-mediated diseases but also on its role on female health and quality of life. Health-care providers' education and the increased awareness of the public on the benefits of the timely estrogen replacement therapy are of utmost importance if we are to provide adequate care for the millions postmenopausal and oophoroectomized women worldwide. Whether estrogen is a friend or a foe, as far as the published evidence has shown so far, it appears to be a woman's best friend.

Disclosure statement

No potential conflict of interest was reported by the authors.

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