Is HRT a trigger for cancer in postmenopausal patients with a history of endometriosis?

Dear Editor,

We read the article entitled "management of menopause in women with a history of endometriosis" by Akgün et al. (1) with a great deal of interest. The authors discussed the hormone replacement therapy (HRT) options, indications, and contraindications in postmenopausal patients with endometriosis. Furthermore, a recently published prospective cohort study examined the relationship between endometriosis and fibroids and the risk of premature mortality, highlighting the importance for primary care providers to consider these gynecological disorders in their assessment of women's health (2). Barnard et al. (3) investigated the relationship between endometriosis typology and ovarian cancer risk. Ovarian cancer risk was highest in women with deep infiltrating endometriosis and/or ovarian endometriomas for all ovarian cancers. These authors recommended counseling regarding ovarian cancer risk and prevention (3).

As mentioned by Akgün et al. (1), endometriosis is a hormone-dependent condition and residual or recurrent endometriotic lesions might still be found in menopause. In this scenario, we would like to ask whether HRT might increase the risk of malignancy. A recent meta-analysis reported that the risk of ovarian malignancy, especially for serous histological type, increased with prolonged exposure time, especially when estrogen replacement therapy (ERT) exceeded 10 years. In the same meta-analysis, it was recommended that long-time users should consider continuous estrogen-progesterone replacement therapy (EPRT) as a safer alternative (4).

Moreover, Lee et al. (5) analyzed a database of ten cancers (cervical, uterine, ovarian, breast, colon, stomach, liver, lung, pancreas, and thyroid) and showed that HRT was a significant risk factor for uterine cancer, but decreased the risk of liver and thyroid cancer while ERT decreased the risks of breast and lung cancers significantly. In the same study, tibolone was not associated with the risk of any of the cancers assessed. Finally, the same group of researchers clarified in another meta-analysis that, although the use of ERT was found to be a significant risk factor for ovarian cancer, after adjusting for co-variables, HRT use, duration of HRT, EPRT and tibolone were not found to be associated with increased risk of developing ovarian cancer (6). The practical implications for clinical decision-making and a clearer differentiation of risks associated with ERT, EPRT, and tibolone would further enhance its impact.

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References

1. Akgün N, Sarıdoğan E. Management of menopause in women with a history of endometriosis. J Turk Ger Gynecol Assoc. 2024; 25: 107-1.
2. Wang YX, Farland LV, Gaskins AJ, Wang S, Terry KL, Rexrode KM, et al. Endometriosis and uterine fibroids and risk of premature mortality: prospective cohort study. BMJ. 2024; 387: e078797.
3. Barnard ME, Farland LV, Yan B, Wang J, Trabert B, Doherty JA, et al. Endometriosis typology and ovarian cancer risk. JAMA. 2024; 332: 482-89.
4. Xiang H, Wang L, Sun L, Xu S. The risk of ovarian cancer in hormone replacement therapy users: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2024; 15: 1414968.
5. Lee HJ, Lee B, Choi H, Lee M, Lee K, Lee TK, et al. Hormone replacement therapy and risks of various cancers in postmenopausal women with de novo or a history of endometriosis. Cancers (Basel). 2024; 16: 809.
6. Lee HJ, Lee B, Choi H, Kim T, Kim Y, Kim YB. Impact of hormone replacement therapy on risk of ovarian cancer in postmenopausal women with de novo endometriosis or a history of endometriosis. Cancers (Basel). 2023; 15: 1708.

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Author's Response

Dear Editor,

We thank Iavazzo and Gkegkes for their interest in our review on "management of menopause in women with a history of endometriosis" and reiterating the messages in it (1). As Iavazzo and Gkegkes highlight, the messages in our review have been further supported by additional epidemiological evidence since the preparation of our review. Wang et al. (2) analysed the risk of premature mortality in women with a history of laparoscopically confirmed endometriosis based on data from Nurses' Health Study II and found that laparoscopically confirmed endometriosis was associated with an increased risk of premature deaths (deaths before age 70 years), mainly driven by increased gynaecological malignancies, along with non-malignant mortality caused by respiratory disorders, senility and ill-defined diseases and diseases of the central nervous system and sense organs. These findings add a new dimension to our messages that women with endometriosis are at greater risk of cardiovascular disease, hypercholesterolemia and osteoporosis. They support our main conclusion that hormone replacement therapy (HRT) should be recommended to women who have a history of endometriosis, when they become menopausal at an early age, at least until the age of natural menopause (1). This approach is likely to improve their quality of life and may reduce the increased morbidity and mortality that the new data show in this group of women.

The article by Xiang et al. (3) is suggestive of increased risk of ovarian cancer in users of HRT who have a history of endometriosis, although more recent studies indicate the risk is minimal. The article by Lee et al. (4) is suggestive of an increase in the risk of uterine cancer but not ovarian cancer, and a decrease in the risks of liver and thyroid cancers in estrogen/progesterone users and in the risk of breast cancer in estrogen-only users. These studies indicate that there are still methodological challenges in analysing the risk of cancer in HRT users and demonstrate that further research is needed with a more robust design.

We reiterate our assertion that combined HRT with estrogen and progesterone, or tibolone should be used in women with a history of endometriosis, even after a hysterectomy, as this approach may reduce the risk of malignant transformation and disease reactivation. Future research may shed some light on the potential benefits and risks of HRT in the long-term. It is necessary to determine whether HRT contributes to the increased premature mortality due to increased gynaecological malignancies.

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References

1. Akgün N, Sarıdoğan E. Management of menopause in women with a history of endometriosis. J Turk Ger Gynecol Assoc. 2024; 25: 107-11.
2. Wang YX, Farland LV, Gaskins AJ, Wang S, Terry KL, Rexrode KM, et al. Endometriosis and uterine fibroids and risk of premature mortality: prospective cohort study. BMJ. 2024; 387: e078797.
3. Xiang H, Wang L, Sun L, Xu S. The risk of ovarian cancer in hormone replacement therapy users: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2024; 15: 1414968.
4. Lee HJ, Lee B, Choi H, Lee M, Lee K, Lee TK, et al. Hormone replacement therapy and risks of various cancers in postmenopausal women with de novo or a history of endometriosis. Cancers (Basel). 2024; 16: 809.