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Review Article

Prescription of Menopausal Hormone Therapy (HRT) in Gynaecological Malignancies: An Evidence-Based Review

Jayalath JAVS[1], Mahanama MGGLO, Hewawitharana KG[2]

[1]*Consultant Obstetrician and Gynaecologist, Teaching Hospital Kalutara, Sri Lanka*

[2]*Acting Consultant Obstetrician and Gynaecologist, Base Hospital Minuwangoda, Sri Lanka*

Corresponding Author: Jayalath JAVS, email - sharadajayalath@yahoo.com

Abstract

Advances in the management of gynaecological malignancies have resulted in improved survival, shifting clinical focus toward long-term quality of life (1,2). Menopause, whether natural or treatment-induced, is common among survivors and may be associated with significant vasomotor symptoms, genitourinary syndrome of menopause (GSM), and long-term consequences of estrogen deficiency (3,4). Historically, menopausal hormone therapy (HRT) has been avoided in women with a history of gynaecological cancer due to concerns regarding disease recurrence (5). This review summarises current evidence on the safety and effectiveness of systemic and local HRT following treatment for gynaecological malignancies and provides an evidence-based, individualised approach to clinical decision-making.

Key words: Menopause, Menopausal hormone therapy, Gynaecological malignancies

Introduction

The majority of gynaecological malignancies occur in postmenopausal women; however, up to 30–40% present in premenopausal or perimenopausal women. Two distinct groups of survivors experience menopausal symptoms: women with a history of gynaecological cancer who subsequently develop natural menopause, and women who experience premature or surgical menopause as a consequence of cancer treatment (6). Treatment-induced menopause can result in severe vasomotor symptoms, sexual dysfunction, osteoporosis, cardiovascular disease, and reduced quality of life (7).

Despite improving survival rates, clinicians remain reluctant to prescribe HRT following gynaecological cancer. Current evidence suggests that a history of gynaecological malignancy is not an automatic contraindication to HRT, and decisions should be individualised, taking into account tumour type, stage, hormone receptor status, patient age, symptom burden, and comorbidities.

In Sri Lanka, where community-based data on menopausal health remain limited, the use of hormone replacement therapy (HRT) in women with a history of gynaecological malignancies represents an important yet underexplored aspect of postmenopausal care (8).

Endometrial Cancer

Endometrial cancer is the most common malignancy of the female genital tract, with five-year survival rates of 80–90% due to early presentation (1). Approximately 20–25% of cases occur in premenopausal women (9). Type I endometrial cancers are estrogen-dependent endometrioid tumours, while Type II cancers are estrogen-independent and associated with poorer prognosis.

Traditionally, HRT was avoided because of concerns regarding stimulation of residual disease (10). Evidence remains limited, but available data do not suggest an increased risk of recurrence in early-stage disease. A randomised controlled trial including 1,236 women with FIGO stage I–II disease demonstrated no significant difference in recurrence rates between estrogen users and placebo during 36 months of follow-up (RR 1.17, 95% CI 0.54–2.50) (11). A Cochrane review incorporating this trial and observational studies concluded that there is insufficient high-quality evidence but no indication of increased recurrence with HRT following surgical treatment of early-stage disease (12). More recent narrative and guideline updates support cautious use of HRT in early-stage, low-grade disease following definitive surgery, while systemic HRT is not recommended in advanced or high-risk histologies (13,14). Low-dose vaginal estrogen appears safe and effective for GSM in endometrial cancer survivors (15).

Uterine Sarcomas

Uterine sarcomas are rare but aggressive tumours. Leiomyosarcomas and endometrial stromal sarcomas frequently express estrogen and progesterone receptors and are considered hormone sensitive. Consequently, systemic HRT is generally not recommended. In exceptional cases with severe symptoms unresponsive to non-hormonal therapies, HRT may be considered following specialist consultation and thorough risk–benefit discussion.

Ovarian Cancer

Approximately 20% of women with epithelial ovarian cancer (EOC) are premenopausal at diagnosis, and treatment often results in abrupt menopause (16). Estrogen receptor expression is common, particularly in serous and endometrioid tumours.

High-Grade Serous Ovarian Carcinoma

Evidence from randomised and observational studies suggests that HRT does not increase recurrence risk in women treated for high-grade serous ovarian carcinoma. A Cochrane review including three studies (350 women) found that HRT may slightly improve overall survival (HR 0.71, 95% CI 0.54–0.93) with little or no effect on progression-free survival (17). A 2023 meta-analysis of eight studies involving 3,578 patients further demonstrated a modest benefit in overall and progression-free survival among HRT users, without differences by age, stage, or grade (18). EMAS and IGCS guidance supports the cautious use of systemic HRT for vasomotor symptoms in this group, while vaginal estrogen is appropriate for GSM (14,19).

Low-Grade Serous Ovarian Carcinoma

Low-grade serous ovarian carcinoma is hormone sensitive, and anti-estrogen therapy is commonly used in recurrent disease (20). There are no robust trials assessing HRT safety in this subgroup. International guidance advises against systemic HRT in FIGO stage II–IV or recurrent disease, while non-hormonal options should be prioritised even in stage I disease (14,19). Vaginal estrogen may be considered for GSM in early-stage disease (19).

Non-Serous Epithelial Ovarian Cancers

Data on non-serous tumours are limited. A retrospective cohort study of 357 women with clear cell, mucinous, and endometrioid ovarian cancers found no adverse impact of HRT on overall or progression-free survival (21). In endometrioid ovarian cancer, HRT may be considered following treatment for FIGO stage I disease but is not recommended when residual or advanced disease is present (14). Vaginal estrogen can be used for GSM across non-serous subtypes (19).

Low-Grade Serous Ovarian Carcinoma

Low-grade serous tumours are hormone sensitive, and anti-estrogen therapy is commonly used. HRT is not recommended in advanced or recurrent disease. In FIGO stage I disease, HRT is not contraindicated but non-hormonal options should be prioritised.

Vaginal estrogen may be used for GSM in early-stage disease.

Non-Serous Epithelial Ovarian Cancers

Evidence suggests no adverse impact of HRT on survival in non-serous tumours, including clear cell and mucinous cancers. In endometrioid ovarian cancer, HRT may be considered in early-stage disease but is not recommended when residual or advanced disease is present. Vaginal estrogen can be used for GSM across non-serous subtypes.

Borderline Ovarian Tumours and Germ Cell Tumours

Borderline ovarian tumours frequently affect younger women. Following complete surgical excision, systemic HRT is recommended for symptomatic women. Germ cell tumours typically affect adolescents and young women; HRT is appropriate following bilateral oophorectomy when required.

Granulosa Cell Tumours

Granulosa cell tumours are estrogen-producing and hormone sensitive. Limited evidence suggests HRT may be cautiously considered in stage I disease following specialist input. HRT is contraindicated in advanced or recurrent disease, while vaginal estrogen may be used for GSM.

Cervical, Vaginal, and Vulval Cancers

Cervical and vaginal cancers are not hormone dependent, and HRT is not contraindicated following treatment (22). A randomised controlled trial of 120 women under 45 years treated for cervical cancer showed no difference in disease-free interval or overall survival between HRT users and controls, with significant improvement in menopausal and radiation-related symptoms in the HRT group (23). Studies evaluating estrogen and progesterone receptor expression in cervical adenocarcinoma demonstrate no correlation with recurrence or survival, supporting the oncological safety of HRT in this population (24).

For women who have undergone hysterectomy and bilateral salpingo-oophorectomy, estrogen-only HRT is recommended. After pelvic radiotherapy with an intact uterus, continuous combined HRT or tibolone is advised (25). Vaginal estrogen is effective for GSM.

The majority of vulval cancers are squamous cell carcinomas and are not hormone sensitive. There is no contraindication to initiating or continuing HRT following treatment, and local estrogen may be beneficial for vulvovaginal symptoms, particularly after radiotherapy (25).

Breast Cancer

In contrast to gynaecological malignancies, systemic HRT is contraindicated in women with hormone-sensitive breast cancer. A 2022 meta-analysis of four randomised controlled trials including over 4,000 patients demonstrated a significantly increased risk of breast cancer recurrence with systemic HRT (HR 1.46, 95% CI 1.12–1.91), with a higher risk observed in hormone receptor–positive disease (26).

Guidelines from the American Society of Clinical Oncology (ASCO), NICE, and ACOG recommend non-hormonal therapies such as SSRIs/SNRIs, gabapentin, clonidine, and cognitive behavioural therapy for vasomotor symptoms (27–29). Low-dose vaginal estrogen may be considered for severe GSM unresponsive to non-hormonal measures, following specialist consultation and shared decision-making (28,29).

Recommended Treatment Principles

HRT should be prescribed at the lowest effective dose for the shortest duration, preferably initiated before age 60 or within ten years of menopause (30). Transdermal estrogen is preferred, and progestogens are required in women with an intact uterus. Vaginal estrogen is effective and safe for GSM in most gynaecological cancer survivors.

Unscheduled bleeding following HRT in gynaecolgical cancer survivors

In women with a history of gynaecological malignancy, the use of hormone replacement therapy requires particular vigilance regarding unscheduled bleeding, which must always prompt thorough assessment. Although HRT may be safely used in selected cancer survivors, unscheduled bleeding should not be attributed to therapy without exclusion of recurrent or new malignancy, especially in endometrial and cervical cancer survivors. Initial evaluation should include a detailed history of HRT regimen and compliance, pelvic examination, and appropriate investigations such as transvaginal ultrasound and endometrial sampling where indicated. Management should be guided by the underlying cause, with adjustment or temporary cessation of HRT once malignancy is excluded, and close multidisciplinary follow-up to ensure both oncological safety and effective symptom control (31)

Conclusion

A diagnosis of gynaecological malignancy is not an absolute contraindication to menopausal hormone therapy (1,5). With careful patient selection, informed counselling, and multidisciplinary input, HRT can significantly improve quality of life for many survivors (6). Ongoing assessment of menopausal symptoms and access to specialist menopause services are essential components of survivorship care. Table 1 shows the summery recommendations of the current review.

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Table 01: Summary Recommendations for HRT Use After Gynaecological Malignancies

Cancer type	Systemic HRT for VMS	Vaginal estrogen for GSM	Key notes	Key references
Endometrial cancer (Stage I–II, low grade, endometrioid)	May be considered with caution	Recommended	Individualised discussion; avoid in high-risk histology	9,10,11,12
Endometrial cancer (Stage III–IV / high-risk histology)	Contraindicated	Use with caution	Limited evidence; avoid systemic HRT	10–12
Uterine leiomyosarcoma	Generally contraindicated	Use with caution	Hormone-sensitive tumour	11,12
Endometrial stromal sarcoma	Contraindicated	Use with caution	Strong hormone sensitivity	11,12
High-grade serous ovarian carcinoma	May be considered	Recommended	No increased recurrence; possible OS benefit	15–17
Low-grade serous ovarian carcinoma (Stage I)	Avoid if possible	May be considered	Prefer non-hormonal options	17,18
Low-grade serous ovarian carcinoma (Stage II–IV / recurrent)	Contraindicated	Avoid	Estrogen-suppressive therapy preferred	17,18
Non-serous epithelial ovarian cancer (Stage I)	May be considered	Recommended	Limited but reassuring data	19
Borderline ovarian tumours (complete excision)	Recommended	Recommended	Young women; premature menopause common	17
Germ cell tumours	May be considered if needed	Recommended	Usually ovarian-sparing surgery	17
Granulosa cell tumour (Stage I)	Use with extreme caution	May be considered	Specialist input required	11,12
Granulosa cell tumour (Stage II–IV / recurrent)	Contraindicated	Avoid	Hormone-sensitive tumour	11,12
Cervical cancer	Recommended	Recommended	Not hormone dependent	21,23
Vaginal cancer	Recommended	Recommended	Not hormone dependent	20,23
Vulval cancer	Recommended	Recommended	Not hormone dependent	23
Breast cancer (HR-positive)	Contraindicated	Selected cases only	Specialist supervision required	24–27

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