Menopause hormone therapy in women treated for rare ovarian tumors: Guidelines from the French national network dedicated to rare gynaecological cancer

Rousset-Jablonski C, Selle F, Adda-Herzog E, Planchamp F, Selleret L, Pomel C, Daraï E, Chabbert-Buffet N, Pautier P, Trémollières F, Guyon F, Rouzier R, Laurence V, Chopin N, Faure-Contier C, Bentivegna E, Vacher-Lavenu MC, Lhomme C, Floquet A, Treilleux I, Lecuru F, Gouy S, Kalbacher E, Genestie C, de la Motte Rouge T, Ferron G, Devouassoux M, Kurtz JE, Namer M, Joly F, Pujade-Lauraine E, Grynberg M, Querleu D, Morice P, Gompel A, Ray-Coquard I.

Introduction : Indications and contraindications for menopause hormone therapy or hormone replacement therapy (HRT) after rare ovarian tumors are frequent issues in clinical practice.

Methods A formalized consensus method was used, in the context of insufficient literature with strong level of evidence, and of contradictory data. A panel of **39 experts from different specialties** (medical oncology, gynecological surgeons, medical gynecologists, specialists in reproductive medicine, endocrinologists, pathologists, pediatric oncologists) contributed to the preparation of the guidelines, following the **DELPHI method**. **Statements were drafted** after a **systematic literature review**, and then **rated through two successive rounds**. After these two rounds, a total of **13 statements finally obtained an acceptable degree of consensus** and constituted the recommendations.

Results Age at menopause, climacteric syndrome, cardiovascular risk, and bone mineral density are criteria taken into account to discuss an HRT prescription. Overall, **prudence has been recommended in the case of potentially hormone-sensitive tumors** such as **sex cord tumors, serous and endometrioid low-grade adenocarcinomas**. In women previously treated for a **high risk serous borderline tumor** (micropapillary pattern, stromal microinvasion, peritoneal implants), **prudence and individual benefit-risk balance** evaluation before prescribing HRT has been recommended. In this case, the risk of invasive recurrence (low grade serous adenocarcinoma), potentially hormone-sensitive, is not negligible indeed. In contrast, **mucinous borderline tumor, and Germ Cell Tumors (GCTs) are considered as hormone-independent tumors**.

13 recommendations

1. Indications for potential conservative surgery in order to avoid iatrogenic premature menopause are mostly depending on oncological indication.
2. The choice of HRT type (estrogen only or estroprogestin) should take into account the context (history of hysterectomy, familial breast cancer risk). In women without history of hysterectomy, progestin should be associated to estrogens. In women with a history of hysterectomy, estroprogestin treatment is not contra-indicated, although, estrogen-only should be the first line choice.
3. The HRT should be introduced after the end of adjuvant treatment.
4. Contraindications for phytoestrogens are the same as those for estrogen-containing HRT.
5. Local estrogens are not contra-indicated, except in women treated with aromatase inhibitors. In this situation, their use is not recommended.
6. **An HRT can be prescribed in women with a history of mucinous borderline tumors, or of serous borderline tumors without any histological high risk criteria.**
7. **In women previously treated for a high risk serous borderline tumor** (micropapillary pattern, stromal microinvasion, peritoneal implants), **individual benefit-risk balance evaluation before prescribing HRT** and case to case discussion in a multidisciplinary team meeting is recommended.
8. **An HRT can be prescribed in women with a history of GCT.**
9. HRT is **contraindicated in women previously treated for sex cord tumors (except in case of granulosa cells tumors stade IA/IB – see recommendation 10)**
10. **In women previously treated for a granulosa cells tumor stade IA/IB, HRT prescription should be discussed on a case to case basis** in a multidisciplinary team meeting.
11. **An HRT can be prescribed in women with a history of mucinous, clear cells or high grade serous adenocarcinomas.**
12. **HRT is contraindicated in women previously treated for low-grade serous adenocarcinoma stade >IA/B.**
13. **In women previously treated for a low-grade serous stade IA/IB, HRT prescription should be discussed on a case to case basis** in a multidisciplinary team meeting.

Conclusion In the context of a scarce literature, a formal consensus method allowed the elaboration of guidelines, which will help clinicians in the management of these patients.