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Current Perspective

# Fertility preservation, contraception and menopause hormone therapy in women treated for rare ovarian tumours: guidelines from the French national network dedicated to rare gynaecological cancers

Christine Rousset-Jablonski [a,b,*], Fréderic Selle [c], Elodie Adda-Herzog [d], François Planchamp [e], Lise Selleret [f], Christophe Pomel [g], Emile Daraï [f], Nathalie Chabbert-Buffet [f], Patricia Pautier [h], Florence Trémollières [i], Frederic Guyon [e], Roman Rouzier [j], Valérie Laurence [j], Nicolas Chopin [a], Cécile Faure-Conter [a], Enrica Bentivegna [h], Marie-Cécile Vacher-Lavenu [k], Catherine Lhomme [h], Anne Floquet [e], Isabelle Treilleux [a], Fabrice Lecuru [l], Sébastien Gouy [h], Elsa Kalbacher [m], Catherine Genestie [h], de la Motte Rouge Thibault [n], Gwenael Ferron [o], Mojgan Devouassoux [p], Jean-Emmanuel Kurtz [q], Magali Provansal [r], Moise Namer [s], Florence Joly [t], Eric Pujade-Lauraine [u], Michael Grynberg [v], Denis Querleu [j], Philippe Morice [h], Anne Gompel [w], Isabelle Ray-Coquard [a,b,x]

[a] *Leon Berard Cancer Center, 28 Rue Laënnec, 69008, Lyon, France*
[b] *Université Claude Bernard Lyon 1, EA 7425 Hesper, Health Service and Performance Research, Domaine Rockefeller, 8 Avenue Rockefeller, 69373, Lyon Cedex 8, France*
[c] *Groupe Hospitalier Diaconesses Croix Saint Simon, 12-18 Rue Du Sergent Bauchat, 75012, Paris, France*
[d] *Hôpital Foch, Service de Gynécologie-Obstétrique, 40 Rue Worth, 92151, Suresnes, France*
[e] *Bergonié Institute Cancer Center, 229 Cours de L'Argonne, 33000, Bordeaux, France*
[f] *Hôpital Tenon, Service de Gynécologie-Obstétrique et Médecine de La Reproduction, 4 Rue de La Chine, 75020, Paris, France*
[g] *Jean Perrin Cancer Center, 58 Rue Montalembert BP 392, 63011, Clermont-Ferrand Cedex 1, France*
[h] *Gustave Roussy Cancer Center, 114 Rue Edouard Vaillant, 94800, Villejuif, France*
[i] *Hôpital Paule de Viguier, Centre de Ménopause et de Dépistage de L'Ostéoporose 330, Avenue de Grande-Bretagne, TSA 70034, 31059, Toulouse Cedex 9, France*
[j] *Curie Institute Cancer Center, 26 Rue D'Ulm, 75005, Paris, France*
[k] *Hôpital Cochin-Port Royal, 53 Avenue de L'Observatoire, 75014, Paris, France*
[l] *Hôpital Européen Geroges Pompidou, 20 Rue Leblanc, 75015, Paris, France*
[m] *CHU Besançon Jean Minjoz, 3 Bd Alexandre Fleming, 25030, Besancon, cedex, France*
[n] *Eugene Marquis Cancer Center, Avenue de La Bataille Flandres-Dunkerque, 35000, Rennes, France*

* *Corresponding author*: Centre Léon Bérard, 28 rue Laënnec, 69008, Lyon, France. Fax: +33 4 78.78.27.01.
*E-mail address:* christine.rousset-jablonski@lyon.unicancer.fr (C. Rousset-Jablonski).

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[o] Claudius Regaud Cancer Center, IUCT Oncopole, 1 Av. Irène Joliot-Curie, 31100, Toulouse, France
[p] Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, 165, Chemin Du Grand Revoyet, 69495, Pierre-Bénite Cedex, France
[q] CHU de Strasbourg, Hôpital de Hautepierre, Avenue Molière, 67200, Strasbourg, France
[r] Paoli-Calmette Institute, 232 Sainte-Marguerite Boulevard, 13009, Marseille, France
[s] Recommandations pour La Pratique Clinique, Nice-Saint-Paul, 06000, France
[t] François Baclesse Cancer Center, 3 Avenue Du Général Harris, 14076, Caen Cedex 5, France
[u] CHU Paris Centre - Hôpital Hôtel-Dieu, 1 Place Du Parvis Notre-Dame, 75004, Paris, France
[v] Hôpital Jean Verdier, Avenue Du 14 Juillet, 93140, Bondy, France
[w] Université Paris-Descartes, 12 Rue de L'école de Médecine, 75006, Paris, France
[x] Groupe GINECO, France

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Rare ovarian tumour;
Delphi method

**Abstract** ***Introduction:*** Rare ovarian tumours include complex borderline ovarian tumours, sex-cord tumours, germ cell tumours and rare epithelial tumours. Indications and modalities of fertility preservation (FP), infertility management, contraindications for hormonal contraception or menopause hormone therapy are frequent issues in clinical practice. A panel of experts from the French national network dedicated to rare gynaecological cancers, and experts in reproductive medicine and gynaecology have built guidelines on FP, contraception and menopause hormone therapy in women treated for ovarian rare tumours.
***Material and methods:*** A panel of 35 experts from different specialties contributed to the preparation of the guidelines, following the DELPHI method (formal consensus method). Statements were drafted after a systematic literature review and then rated through two successive rounds.
***Results:*** Thirty-five recommendations were identified, concerning indications for FP, contraindications for ovarian stimulation, contraceptive options and menopause hormone therapy for each tumour type.
***Discussion:*** Overall, caution has been recommended in the case of potentially hormone-sensitive tumours such as sex-cord tumours, serous and endometrioid low-grade adenocarcinomas, as well as for high-risk serous borderline ovarian tumours.
***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.


## 1. Introduction

Rare ovarian tumours include complex borderline ovarian tumours, sex-cord, germ cells and rare epithelial tumours. Premenopausal women management include specific issues such as fertility preservation (FP), contraception and premature menopause management. However, some of these tumours are hormone-sensitive, and the impact of controlled ovarian stimulation (COS), hormonal contraception or hormone replacement therapy (HRT) on recurrence risk should be taken into account.

A panel of experts from the French national network dedicated to rare gynaecological cancers have worked on guidelines about FP, infertility management, contraception and HRT in women treated for ovarian rare tumours.

## 2. Material and methods

The Delphi method, a formalized consensus method, was used, in the context of insufficient literature with strong level of evidence [1]. Thirty-five French experts (oncologists, surgeons, medical gynaecologists, reproductive medicine specialists, endocrinologists, pathologists and paediatric oncologists) participated. After a systematic literature review, written statements were drafted for circulation to all participants. Two rounds of the Delphi survey were conducted (Table 1) [2]. Thirty-five statements finally obtained an acceptable degree of consensus [2] and constituted the recommendations (Tables 2 and 3).

Table 1
Delphi methodology: degree of agreement assessment.

| First round of rating | | | | | |
|---|---|---|---|---|---|
| Proposal | Agreement among experts Degree | Median | | Distribution of scores | Need for a second round of rating |
| Appropriate | Strong agreement | ≥7 | [7–9] | | No, proposal accepted as it is |
| | Relative agreement | ≥7 | [5–9] | | Yes |
| Inappropriate | Strong agreement | ≤3 | [1–3] | | No, proposal rejected as it is |
| | Relative agreement | ≤3.5 | [1–5] | | Yes |
| Uncertain | Undecided | [4–6.5] | [1–9] | | Yes |
| | No consensus | / | Other situations | | Yes |
| Second round of rating | | | | | |
| Proposal | Agreement among experts Degree | Median | Distribution of scores | | Final decision |
| Appropriate | Strong agreement | ≥7 | All scores are between 7 and 9, except 2 missing values or 2 excluded values (<7) or 1 missing value and 1 excluded value | | Proposal accepted |
| | Relative agreement | ≥7 | All scores are between 5 and 9, except 2 missing values or 2 excluded values (<5) or 1 missing value and 1 excluded value | | Proposal accepted |
| Inappropriate | Strong agreement | ≤3 | All scores are between 1 and 3, except 2 missing values or 2 excluded values (>3) or 1 missing value and 1 excluded value | | Proposal rejected |
| | Relative agreement | ≤3.5 | All scores are between 1 and 5, except 2 missing values or 2 excluded values (>5) or 1 missing value and 1 excluded value | | Proposal rejected |
| Uncertain | Other situations | | – | | Proposal rejected |

Experts were asked to rate, using a scale from 1 (strongly disagree) to 9 (strongly agree) each statement. The rankings were summarised and assessed for degree of agreement. If an acceptable degree of consensus was obtained, the process ceased. All statements that did not reach sufficient agreement were selected for a second round Participants reranked their agreement with each statement in the questionnaire, with the opportunity to change their score in view of the group's response and the changes made in the statement.

## 3. General recommendations

### 3.1. FP and infertility management after rare malignant ovarian tumour

Following national bioethics laws and good clinical practice recommendations, a specific information on infertility risks and on FP options should be implemented *(recommendation 1 (R1) and 2(R2))*. COS followed by oocyte or embryo vitrification should be proposed whenever possible [3]. COS is contraindicated in some situations, considering the potential risk of gonadotropins and hyperoestrogenism on the disease recurrence. In these cases, alternative FP methods (immature oocytes retrieval or ovarian cortex cryopreservation [4]) or assisted reproductive technology methods (natural-cycle *in-vitro* fertilization or *in-vitro* maturation) should be used. Ovarian cortex cryopreservation offers significant pregnancy rates [5], but the risk of re-implanting pre-existing cancer cells should be considered [6].

### 3.2. Contraception during oncological treatment

Combined oestroprogestin contraception increases thromboembolic risk [7] and thus should be avoided *(R29)*. In contrast, progestin alone can be used [8] *(R30)*. Previously inserted intrauterine device can be left in, as infection risk is transient following its insertion *(R28)*. Barrier methods can be proposed. GnRH agonists can ultimately be used if other methods are contraindicated or not acceptable *(R31)*.

### 3.3. Menopause and HRT

Conservative surgeries are mostly depending on oncological strategy *(R15)*. HRT can prevent some morbidity and excess mortality [9] associated with

Table 2
Recommendations.

| Recommendation number | | Degree of agreement |
|---|---|---|
| **General recommendations (not depending on the tumoural type)** | | |
| *FP and infertility management* | | |
| 1 | A specific information on infertility risks and on fertility preservation options should be discussed for every patient before a treatment potentially impairing fertility. | Strong |
| 2 | An ovarian reserve evaluation (pelvic ultrasound with antral follicle count and anti-Mullerian hormone test) and viral serologies should be performed either before or during the oncofertility consultation | Strong |
| *Menopause and HRT* | | |
| 15 | Indications for potential conservative surgery to avoid iatrogenic premature menopause are mostly depending on oncological indication. | Strong |
| 24 | The choice of HRT type (oestrogen only or oestroprogestin) should take into account the context (history of hysterectomy, familial breast cancer risk). In women without history of hysterectomy, progestin should be associated to oestrogens. In women with a history of hysterectomy, oestroprogestin treatment is not contraindicated, although, oestrogen-only should be the first line choice. | Strong |
| 25 | The HRT should be introduced after the end of adjuvant treatment. | Strong |
| 26 | Contraindications for phytoestrogens are the same as those for oestrogen-containing HRT. | Strong |
| 27 | Local oestrogens are not contraindicated, except in women treated with aromatase inhibitors. In this situation, their use is not recommended. | Relative |
| *Contraception* | | |
| 28 | During cancer treatment, a previously introduced copper intrauterine device can be left in. | Strong |
| 29 | Combined oestroprogestin contraception use is not recommended during cancer treatment (especially during chemotherapy) to avoid a thromboembolic risk increase. | Strong |
| 30 | Progestin-only contraception (progestin-only mini-pill, high-dose antigonadotropic progestins as chlormadinone acetate or cyproterone acetate, contraceptive implant, levonorgestrel containing intrauterine device) are not contraindicated during cancer treatment. | Relative |
| 31 | A GnRH agonist can be used in case of contraindication or intolerance to all the other contraceptive types. | Relative |
| **Borderline ovarian tumours** | | |
| *FP and infertility management* | | |
| 3 | A fertility preservation (eventually including ovarian stimulation) should be discussed in a multidisciplinary team meeting including an expert in reproductive medicine for every woman with a history of bilateral BOT due to its recurrence risk. | Relative |
| 5 | Fertility preservation strategy should be discussed on a case to case basis in a multidisciplinary team meeting in women previously treated for a BOT without any histological high-risk criterion (without any peritoneal implant, micropapillary pattern or microinvasion) and presenting a recurrence. | Relative |
| 7 | Ovarian stimulation for fertility preservation is contraindicated in women previously treated for a BOT with any histological high-risk criterion (with any peritoneal implant, micropapillary pattern or microinvasion) and presenting a recurrence. | Relative |
| 12 | In a woman with a history of BOT with non-invasive implants and/or micropapillary pattern and/or stromal microinvasion and presenting with infertility, the use of ovarian stimulation in the treatment of infertility should be discussed in a multidisciplinary team meeting. | Relative |
| *Contraception* | | |
| 32 | After a conservative treatment of a BOT or a germ cell tumour, all types of hormonal contraceptions can be prescribed. | Strong |
| *Menopause and HRT* | | |
| 17 | An HRT can be prescribed in women with a history of mucinous borderline tumours or of serous borderline tumours without any histological high-risk criterion. | Strong |
| 21 | In women previously treated for a high-risk serous borderline tumour (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. | Relative |
| **Germ cell tumour** | | |
| *FP and infertility management* | | |
| 4 | A fertility preservation (eventually including ovarian stimulation) should be discussed in a multidisciplinary team meeting including an expert in reproductive medicine for every woman with a history of immature teratoma because of its recurrence risk. | Relative |
| 6 | Fertility preservation strategy (eventually including ovarian stimulation) should be discussed on a case to case basis in a multidisciplinary team meeting in women previously treated for an immature teratoma and presenting a recurrence highly suspicious of benign teratoma. | Relative |

| | | |
|---|---|---|
| *Contraception* | | |
| 32 | After a conservative treatment of a BOT or a germ cell tumour, all types of hormonal contraceptions can be prescribed. | Strong |
| *Menopause and HRT* | | |
| 16 | An HRT can be prescribed in women with a history of germ cell tumour. | Strong |
| **Sex-cord tumours** | | |
| *FP and infertility management* | | |
| 9 | In a woman with a history of sex-cord tumour (except in the case of granulosa cells tumour stage IA- see recommendation 13) and presenting with infertility, the use of ovarian stimulation in the treatment of infertility is contraindicated, and assisted reproductive technology without COS should be used. | Relative |
| 13 | In a woman with a history of granulosa cells tumour stage IA and presenting with infertility, the use of ovarian stimulation in the treatment of infertility should be discussed in a multidisciplinary team meeting. | Strong |
| *Contraception* | | |
| 33 | In a woman with a history of conservative surgery for an adult granulosa cells tumour, oestrogen-containing contraceptions are contraindicated. Others hormonal contraceptions can be prescribed. | Relative |
| *Menopause and HRT* | | |
| 19 | HRT is contraindicated in women previously treated for sex-cord tumours (except in case of granulosa cells tumours stage IA/IB: see recommendation 23). | Strong |
| 23 | In women previously treated for a granulosa cells tumour stage IA/IB, HRT indication should be discussed on a case to case basis in a multidisciplinary team meeting. | Strong |
| **Rare epithelial tumours** | | |
| *FP and infertility management* | | |
| 8 | In a woman with a history of low-grade serous adenocarcinoma and presenting with infertility, the use of ovarian stimulation in the treatment of infertility is contraindicated. | Strong |
| 10 | In a woman with a history of low-grade endometrioid adenocarcinoma and presenting with infertility, the use of ovarian stimulation in the treatment of infertility is contraindicated. | Relative |
| 11 | In a woman with a history of infiltrative mucinous adenocarcinoma and presenting with infertility, the use of ovarian stimulation in the treatment of infertility is contraindicated. | Strong |
| 14 | In a woman with a history of expansive mucinous adenocarcinoma and presenting with infertility, the use of ovarian stimulation in the treatment of infertility should be discussed in a multidisciplinary team meeting. | Strong |
| *Contraception* | | |
| 34 | After a conservative treatment of a mucinous adenocarcinoma or of a high-grade serous or endometrioid adenocarcinoma, all types of hormonal contraceptions can be prescribed. | Relative |
| 35 | After a conservative treatment of a low-grade serous or endometrioid adenocarcinoma, the use of hormonal contraception is not recommended. | Relative |
| *Menopause and HRT* | | |
| 18 | An HRT can be prescribed in women with a history of mucinous, clear cell or high-grade serous adenocarcinomas. | Relative |
| 20 | HRT is contraindicated in women previously treated for low-grade serous adenocarcinoma stage > IA/B. | Strong |
| 22 | In women previously treated for a low-grade serous stage IA/IB, HRT prescription should be discussed on a case to case basis in a multidisciplinary team meeting. | Relative |

BOT, borderline ovarian tumour; FP, fertility preservation; HRT, hormone replacement therapy.

Table 3
Summary of recommendations on controlled ovarian stimulation in the treatment for infertility, hormonal contraception and menopause hormone therapy.

| | | Controlled ovarian stimulation in the treatment for infertility | Hormonal contraception | Menopause hormone therapy |
|---|---|---|---|---|
| Borderline ovarian tumour | | Without any histological high-risk criteria[a]: possible<br>With histological high-risk criteria[a]: to be discussed on a case to case basis | Possible | Serous borderline ovarian tumour without any peritoneal implant: possible<br>Mucinous borderline: possible<br>Serous borderline ovarian tumour with peritoneal implants: to be discussed on a case to case basis |
| Germ cells tumour | | Possible | Possible | Possible |
| Sex-cord tumours | | Granulosa stage IA: to be discussed on a case to case basis<br>Other situations: contraindicated | Adult granulosa: oestrogens-containing contraceptions contraindicated | Granulosa stage IA/B: to be discussed on a case to case basis<br>Other situations: contraindicated |
| Rare epithelial tumours | Low-grade serous adenocarcinoma | Contraindicated | Not recommended | Stage IA/B: to be discussed on a case to case basis<br>Stage > IA/B: contraindicated |
| | Endometrioid adenocarcinoma | Contraindicated | High grade: possible<br>Low-grade: not recommended | |
| | Mucinous adenocarcinoma | Expansive: to be discussed on a case to case basis<br>Infiltrative: contraindicated | Possible | Possible |
| | Clear-cell adenocarcinoma | [b] | [b] | Possible |

[a] High-risk histological criteria: micropapillary pattern, stromal microinvasion, peritoneal implants and mucinous borderline ovarian tumour with intraepithelial carcinoma.
[b] These situations were not discussed as clear-cell adenocarcinoma treatment requires a radical surgery.

premature menopause. When considered, HRT should be introduced after the end of the adjuvant treatment *(R25)*. The choice of HRT type is a multifactorial decision *(R24)*. HRT duration will depend on age at menopause, symptoms, cardiovascular and osteoporotic risks. Considering the lack of data on phytoestrogens, their contraindications are similar to those for HRT *(R26)*. There are no specific data concerning local oestrogens use. Despite a possible low systemic passage, they are rarely contraindicated *(R27)*.

## 4. Specific recommendations

### 4.1. Borderline ovarian tumours

There is a continuum of tumour progression between serous borderline ovarian tumours (BOT) and type I ovarian cancer, especially low-grade serous adenocarcinoma [10], that are hormone-sensitive tumours. Thus, caution is needed in the decisions of using COS or HRT after BOT with invasive peritoneal implants, micropapillary patterns, stromal microinvasion or mucinous tumour with intraepithelial carcinoma. Indeed, these histological features are associated with a higher risk of invasive recurrence [11].

#### 4.1.1. FP and infertility management

Nulliparity, infertility and assisted reproductive technology are associated with a higher risk for BOT [11]. Only few observational studies have reported their experience on assisted reproductive technology after BOT. The recurrence rate (pooled in a meta-analysis) was quite low (23% [95%CI: 6–39%]) [11], with a possible selection bias.

*4.1.1.1. Fertility preservation.* Conservative surgery is the most efficient option to preserve ovarian reserve [11]. At initial management, FP using COS is not allowed before a complete surgical staging.

*4.1.1.1.1. FP in case of recurrent BOT.* Considering the impact of iterative surgeries on ovarian reserve, FP should be discussed before surgery, despite the unavailability of the recurrence histological analysis. Histological characteristics of the initial tumour should be considered to decide if FP using COS is allowed before surgery *(R5, R7)*.

*4.1.1.1.2. FP after BOT treatment.* FP should be considered in women previously treated for a bilateral BOT, considering their risk of ovarian insufficiency *(R3)*. COS use is discussed depending on histological prognostic factors.

*4.1.1.2. Infertility management.* Histological prognostic factors of BOT should be considered to decide if assisted reproductive technology using COS is allowed [11] *(R12)*.

#### 4.1.2. Contraception

Large meta-analyses found a trend to a decrease in serous BOT risk in oral contraception users (mainly oestroprogestins), whereas the incidence of mucinous BOT was not affected [12]. Longer duration of use (more than 5 years) could be associated with a significant decreased risk (odds ratio = 0.60, 95% confidence interval [CI]:0.40–0.93) [13]. Data concerning progestin-only contraceptives are too scarce to allow interpretation [14]. A decrease in ovarian adenocarcinoma risk was found in levonorgestrel intrauterine device users (significant) [15] and in progestin-only mini-pill users (non-significant) [14]. Considering all these indirect reassuring data, all hormonal contraceptions can be used *(R32)*.

#### 4.1.3. Hormone replacement therapy

A prospective cohort study including 150 women previously treated for BOT found no impact on overall survival in HRT users [16].

Beral meta-analysis [17] found a higher risk of serous BOT in past or current users (relative risk = 1.26; 95% CI = 1.01–1.58), whereas the risk of mucinous BOT was reduced [17]. HRT can thus be prescribed after a mucinous or serous BOT without any high-risk criteria *(R17)*, whereas caution is recommended after high-risk serous BOT *(R21)*.

### 4.2. Malignant germ cell tumours

Conservative surgery is often acceptable in non-menopausal women. They are hormone-independent tumours, and there is neither known impact of assisted reproductive technology, COS, hormonal contraception or HRT on the risk of developing germ cells tumours nor on their recurrence risk.

#### 4.2.1. FP and infertility management

Adjuvant chemotherapy—when indicated [18]—has a low gonadotoxicity [19] and should be started promptly. Thus, the benefit-risk benefit balance of FP using COS before chemotherapy seemed unfavourable, and no recommendation was established.

However, FP may be discussed in women previously treated for an immature teratoma *(R4)*. This latter is at high risk of contralateral recurrence [20], further damaging ovarian reserve. Impact of COS on recurrence risk has not been evaluated, but FP using COS is possible as germ cell tumours are hormone insensitive.

In women previously treated for an immature teratoma and presenting a contralateral ovarian cyst

highly suspicious of benign teratoma, a FP using COS can be discussed before surgery on an individual basis (*R6*).

Any assisted reproductive technology including COS can be used in infertile women previously treated for a germ cell tumour.

#### 4.2.2. Contraception and HRT

Despite the absence of specific data, because germ-cell tumours are hormone-insensitive, all types of contraception (*R32*) and HRT can be used (*R16*).

### 4.3. Sex-cord-stromal tumours

Follicle-stimulating hormone (FSH), luteinizing hormone (LH) and oestrogen regulate granulosa cells and/or stimulate their proliferation. GnRH agonists have a partial efficiency in treating advanced granulosa cell tumours [21], presumably mediated through the decrease in LH and FSH levels. High-dose progestin, whose action might be mediated through steroid receptors and their antigonadotropic activity also induce favourable responses [21]. On the other hand, tamoxifen and aromatase inhibitors efficacy [21] also reinforce the idea of a sensitivity to oestrogens of granulosa cell tumours.

Recombinant FSH use and hyperoestrogenism following COS, as well as oestrogens contained in contraceptives or HRT might thus be deleterious after granulosa cell tumour treatment.

Sertoli cells and Leydig cells depend on gonadotropin stimulation as well, and response to GnRH agonists have also been described.

#### 4.3.1. FP and infertility management

The only data published is a case series of 12 granulosa cell tumours discovered after COS [22]. Despite the lack of specific data on sex-cord-stromal tumours and sex-cord-stromal tumour recurrence risks after assisted reproductive technology/COS, the precautionary principle is to avoid COS.

*4.3.1.1. Fertility preservation.* Conservative surgery is acceptable for stage I disease not usually requiring adjuvant chemotherapy. Therefore, the impact on fertility is exclusively because of surgery. No recommendation concerning FP at the time or after the management of a sex-cord-stromal tumour was established. As a rule, COS will only be discussed in a context of a proven infertility after sex-cord-stromal tumour but not in a context of prevention (FP).

*4.3.1.2. Infertility management.* A history of stage IA granulosa cell tumour is the only acceptable situation for discussing COS (*R13*). COS is not recommended in all the other situations (*R9*).

#### 4.3.2. Contraception

There are no data concerning contraception after sex-cord-stromal tumours. Only a case-control study describing a decreased risk of granulosa cell tumours in current or past oral contraception users is available [23]. However, despite specific data, it is reasonable to avoid oestrogen-containing contraceptives after an adult granulosa cell tumour (*R33*). Other hormonal contraceptives are acceptable. High-dose progestins should be preferred, considering their potential beneficial effect [21].

#### 4.3.3. Hormone replacement therapy

There are no data concerning HRT use after sex-cord-stromal tumours. Nevertheless, the potential deleterious impact of oestrogens [21] leads to prudence. HRT can be discussed on an individual basis after an adult granulosa cell tumour stage IA/B (*R23*), but is contraindicated in all the other situations (*R19*).

### 4.4. Rare epithelial ovarian tumours

This tumour group includes low-grade serous, mucinous, endometrioid and clear cells adenocarcinomas. Mucinous and clear cells adenocarcinoma are hormone-independent [24]. In contrast, low-grade serous and endometrioid adenocarcinomas are potentially hormone-sensitive tumours with hormone receptors [25], as confirmed by data on efficiency of antioestrogens [26].

#### 4.4.1. FP and infertility management

Low-grade serous and endometrioid adenocarcinoma stage IA or IC can be managed with conservative surgery. Adjuvant chemotherapy is not systematic. Hence, FP is not indicated, and the expert group only discussed infertility management. Despite the lack of data on assisted reproductive technology after low-grade serous or endometrioid adenocarcinoma, COS was contraindicated considering their hormone-sensitivity (*R8, R10*). Mucinous adenocarcinoma are insensitive to oestrogens and progestins, but the impact of gonadotrophins is unknown. A case of recurrence following ovulation induction was described [27], and safety of COS cannot be assured. COS should thus be discussed on a case-to-case basis in women with a history of expansive mucinous adenocarcinoma (*R14*), whereas it is contraindicated after an infiltrative mucinous adenocarcinoma (*R11*).

#### 4.4.2. Contraception

Epithelial ovarian cancer (all types) risk is decreased in oral contraception ever or current users. Mucinous adenocarcinomas risk was not impacted [12]. In contrast,

the risk of clear cells, endometrioid, and serous (all grades together) adenocarcinomas was significantly decreased in women having used oral contraception for 5 years or more [12]. Any differential impact on the risk of low-grade or high-grade serous adenocarcinoma is not evaluable in available studies. A non-significant decrease in risk has also been found among users of progestin-only mini-pill [14] and of levonorgestrel intrauterine device [15]. As a result, hormonal contraceptives can be used after mucinous, high-grade serous or endometrioid adenocarcinomas *(R34)*. Considering the hormone sensitivity of low-grade serous or endometrioid adenocarcinoma, hormonal contraceptives are not recommended *(R35)*.

#### *4.4.3. Hormone replacement therapy*

A meta-analysis of two randomised and four cohort studies suggested that HRT use after epithelial ovarian cancer could improve overall survival (hazards ratio [HR] = 0.69, 95% CI: 0.61–0.79), without increasing recurrence risk [28]. A recent placebo-controlled randomised study described an improved overall survival (HR = 0.63; 95% CI = 0.44–0.90) and relapse-free survival (HR = 0.67; 95% CI = 0.47–0.97) in HRT users after epithelial ovarian cancer [29]. A retrospective cohort study has specifically studied HRT use after non-serous epithelial ovarian cancer. Disease-free survival was improved (HR = 0.354, 95% CI = 0.17–0.74) in HRT users younger than 55 years. Survival was not evaluated by histological subtype [30]. The largest cohort study included in Li meta-analysis found a better overall survival among HRT users in women with a history of serous (HR = 0.65; 95% CI: 0.44–0.96), clear cells or undifferentiated tumour (HR = 0.23, 95% CI:0.06–0.91). No difference was found in women with mucinous or endometrioid tumours [16]. Low-grade and high-grade tumours were not evaluated separately [16].

Considering the few data available on HRT use after epithelial ovarian cancer by histological subtypes, the data available on the risk of developing an epithelial ovarian cancer in HRT users were also considered. HRT users are at higher risk of serous or endometrioid adenocarcinoma, whereas the risk of mucinous or clear cells tumours is not significantly different [17].

As a result, HRT can be used without restriction after mucinous or clear cells adenocarcinoma *(R18)*. In contrast, despite specific data on HRT use after low-grade serous or endometrioid adenocarcinoma, HRT should not be used after these hormone-sensitive tumours [25,26] *(R20)*, except on a case-to-case basis in stage IA/B diseases *(R22)*.

## 5. Conclusion

In the context of a scarce literature, a formal consensus method allowed the elaboration of guidelines helping clinicians to council women treated or with a history of rare ovarian malignant tumours. COS, hormonal contraceptives, and HRT use depend mainly on the hormone-sensitivity of the disease and on its recurrence risk.

## Conflicts of interest statement

Dr. Rousset-Jablonski reported personal fees from Bayer Healthcare (lectures) and conflicts of interests with Mylan (advisory board without personal fees) and Merck Serono (lecture without personal fees), outside the submitted work. Dr. Gompel reported personal fees from Mithra, outside the submitted work. Dr. Gouy reported conflicts of interest with Roche (consultancy, without personal fees), outside the submitted work. Dr. Chabbert-Buffet reported grants from HRA Pharma, personal fees from Gedeon Richter, Theramex and TEVA, outside the submitted work. Dr. Pujade-Lauraine reported personal fees and non-financial support from AstraZeneca, Roche and Tesaro and personal fees from Clovis, Incyte and Pfizer, outside the submitted work. Dr. Tremollieres reported personal fees from Amgen, Théramex, TEVA and non-financial support from Besins Healthcare France, outside the submitted work. Other authors declared no conflict of interest.

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