



# Préservation de la fertilité, contraception et traitement hormonal de la ménopause chez les femmes traitées pour tumeurs malignes rares de l'ovaire : recommandations du réseau national dédié aux cancers gynécologiques rares (TMRG/GINECO)

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## **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.**

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## **Abstract**

**Introduction** Rare ovarian tumours include complex borderline ovarian tumours, sex-cord tumours, germ cell tumours, rare epithelial tumours. Indications and modalities of fertility preservation, 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 fertility preservation, 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 fertility preservation, 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.

**Key words:** fertility preservation; controlled ovarian stimulation; assisted reproductive technology; hormone replacement therapy; contraception; borderline ovarian tumour; sex cord tumour; germ cell tumour; rare ovarian tumour; Delphi method.

## **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.

## **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, 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).

## **I. General recommendations**

### **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 contra-indicated in some situations, considering the potential risk of gonadotropins, and hyperestrogenism 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].

## **2. Contraception during oncological treatment**

Combined estroprogestin 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 contra-indicated or not acceptable (R31).

## **3. Menopause and HRT**

Conservative surgeries are mostly depending on oncological strategy (R15). HRT can prevent some morbidity and excess mortality [9] associated with 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 contra-indications are similar to those for HRT (R26). There is no specific data concerning local estrogens use. Despite a possible low systemic passage, they are rarely contra-indicated (R27).

# **II. Specific recommendations**

## **1. Borderline Ovarian Tumours (BOT)**

There is a continuum of tumour progression between serous 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].

### **A. 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.

#### **a. FP**

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.

#### **b. 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](#)).

#### **c. 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.

#### **d. Infertility management**

Histological prognostic factors of BOT should be considered to decide if assisted reproductive technology using COS are allowed [11] ([R12](#)).

### **B. Contraception**

Large meta-analyses found a trend to a decrease in serous BOT risk in oral contraception users (mainly estroprogestins), 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 (OR=0.60, 95%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](#)).

### **C. HRT**

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 (RR=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*).

## **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.

### **A. 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.

### **B. Contraception and HRT**

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

## **3. Sex cord-stromal tumours**



FSH, LH and estrogen 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 estrogens of granulosa cell tumors.

Recombinant FSH use and hyperestrogenism following COS, as well as estrogens contained in contraceptives or HRT might thus be deleterious after granulosa cell tumor treatment.

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

### **A. FP and infertility management**

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

#### **a. FP**

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

#### **b. Infertility management**

A history of stage IA granulosa cell tumor is the only acceptable situation for discussing COS ([R13](#)). COS is not recommended in all the other situations ([R9](#)).

### **B. Contraception**

There is no data concerning contraception after sex cord-stromal tumors. Only a case-control study describing a decreased risk of granulosa cell tumors in current or past oral contraception users is available [23]. However, despite specific data, it is reasonable to avoid estrogen-containing contraceptives after an adult granulosa cell tumor ([R33](#)). Other hormonal

contraceptives are acceptable. High-dose progestins should be preferred, considering their potential beneficial effect [21].

### **3. HRT**

There is no data concerning HRT use after sex cord-stromal tumors . Nevertheless, the potential deleterious impact of estrogens [21] leads to prudence: HRT can be discussed on an individual basis after an adult granulosa cell tumor stage IA/B ([R23](#)), but is contra-indicated in all the other situations ([R19](#)).

## **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 antiestrogens [26].

### **A. 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 contra-indicated considering their hormone-sensitivity ([R8](#), [R10](#)). Mucinous adenocarcinoma are insensitive to estrogens 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 contra-indicated after an infiltrative mucinous adenocarcinoma ([R11](#)).

### **B. 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).

### C. HRT

A meta-analysis of 2 randomized and 4 cohort studies suggested that HRT use after epithelial ovarian cancer could improve overall survival (HR =0.69, 95% CI: 0.61–0.79), without increasing recurrence risk [28]. A recent placebo-controlled randomized 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).

### 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. Pr. 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. Pr. Chabbert-Buffet reported grants from HRA Pharma, personal fees from Gedeon Richter, personal fees from Theramex, personal fees from TEVA , outside the submitted work . Pr. PUJADE-LAURINE reported personal fees and non-financial support from Astra-zeneca, personal fees and non-financial support from Tesaro, personal fees from Clovis, personal fees and non-financial support from Roche, personal fees from Incyte, personal fees from Pfizer, outside the submitted work. Pr. TREMOLLIÈRES reported personal fees from Amgen, personal fees from Théramex, personal fees from TEVA, non-financial support from Besins Healthcare France, outside the submitted work. Other authors declared no conflict of interest.

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**Table 1: Delphi methodology: degree of agreement assessment**

<b>FIRST ROUND OF RATING</b>				
<b>Proposal</b>	<b>Agreement among experts Degree</b>	<b>Median</b>	<b>Distribution of scores</b>	<b>Need for a second round of rating</b>
Appropriate	Strong agreement	$\geq 7$	[7-9]	No, proposal accepted as it is
	Relative agreement	$\geq 7$	[5-9]	Yes
Inappropriate	Strong agreement	$\leq 3$	[1-3]	No, proposal accepted as it is
	Relative agreement	$\leq 3.5$	[1-5]	Yes
Uncertain	Undecided No consensus	[4-6.5]	[1-9] Other situations	Yes
<b>SECOND ROUND OF RATING</b>				
<b>Proposal</b>	<b>Agreement among experts Degree</b>	<b>Median</b>	<b>Distribution of scores</b>	<b>Final decision</b>
Appropriae	Strong agreement	$\geq 7$	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	$\geq 7$	All scores are between 5 et 9, except 2 missing values, or 2 excluded values (<5), or 1 missing value and 1 excluded value	Proposal accepted
Inappropriate	Strong agreement	$\leq 3$	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	$\leq 3.5$	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.



**Table 2: Recommendations**

Recommendation number	Degree of agreement
<b>General recommendations (not depending on the tumoral type)</b>	
<i><b>FP and infertility management</b></i>	
<b>1</b>	A specific information on infertility risks and on fertility preservation options should be discussed for every patient before a treatment potentially impairing fertility. Strong
<b>2</b>	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
<i><b>Menopause and HRT</b></i>	
<b>15</b>	Indications for potential conservative surgery in order to avoid iatrogenic premature menopause are mostly depending on oncological indication. Strong
<b>24</b>	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. Strong
<b>25</b>	The HRT should be introduced after the end of adjuvant treatment. Strong
<b>26</b>	Contraindications for phytoestrogens are the same as those for estrogen-containing HRT. Strong
<b>27</b>	Local estrogens are not contra-indicated, except in women treated with aromatase inhibitors. In this situation, their use is not recommended. Relative
<i><b>Contraception</b></i>	

28	During cancer treatment, a previously introduced copper intrauterine device can be left in.	Strong
29	Combined estroprogestin contraception use is not recommended during cancer treatment (especially during chemotherapy) in order 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 contra-indicated during cancer treatment.	
31	A GnRH agonist can be used in case of contra-indication or intolerance to all the other contraceptive types.	Relative
<b>Borderline ovarian tumours</b>		
<i>FP and infertility management</i>		
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 without any histological high-risk criterion (without 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

<b>Contraception</b>		
<b>32</b>	After a conservative treatment of a BOT or a germ cell tumour, all types of hormonal contraceptions can be prescribed.	Strong
<b>Menopause and HRT</b>		
<b>17</b>	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
<b>21</b>	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
<b>Germ cell tumour</b>		
<b>FP and infertility management</b>		
<b>4</b>	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 due to its recurrence risk.	Relative
<b>6</b>	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
<b>Contraception</b>		
<b>32</b>	After a conservative treatment of a BOT or a germ cell tumour, all types of hormonal contraceptions can be prescribed.	Strong
<b>Menopause and HRT</b>		

<b>16</b>	An HRT can be prescribed in women with a history of germ cell tumor.	Strong
<b>Sex cord tumours</b>		
<i>FP and infertility management</i>		
<b>9</b>	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 contra-indicated, and assisted reproductive technology without COS should be used.	Relative
<b>13</b>	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
<i>Contraception</i>		
<b>33</b>	In a woman with a history of conservative surgery for an adult granulosa cells tumour, estrogen-containing contraceptions are contraindicated. Others hormonal contraceptions can be prescribed.	Relative
<i>Menopause and HRT</i>		
<b>19</b>	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
<b>23</b>	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
<b>Rare epithelial tumours</b>		
<i>FP and infertility management</i>		
<b>8</b>	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 contra-indicated.	Strong
<b>10</b>	In a woman with a history of low-grade endometrioid adenocarcinoma, and presenting with infertility, the use	Relative

	of ovarian stimulation in the treatment of infertility is contra-indicated.	
<b>11</b>	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 contra-indicated.	Strong
<b>14</b>	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
<b><i>Contraception</i></b>		
<b>34</b>	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
<b>35</b>	After a conservative treatment of a low-grade serous or endometrioid adenocarcinoma, the use of hormonal contraception is not recommended.	Relative
<b><i>Menopause and HRT</i></b>		
<b>18</b>	An HRT can be prescribed in women with a history of mucinous, clear cell or high-grade serous adenocarcinomas.	Relative
<b>20</b>	HRT is contraindicated in women previously treated for low-grade serous adenocarcinoma stage >IA/B.	Strong
<b>22</b>	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

Table legend :

BOT : borderline ovarian tumor

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	<u>Without any histological high-risk criteria</u> *: possible  <u>With histological high-risk criteria</u> *: to be discussed on a case to case basis	Possible	<u>Serous borderline ovarian tumour without any peritoneal implant</u> : possible  <u>Mucinous borderline</u> : possible  <u>Serous borderline ovarian tumour with peritoneal implants</u> : to be discussed on a case to case basis
	Germ cells tumour	Possible	Possible	Possible
	Sex-cord tumours	<u>Granulosa stage IA</u> : to be discussed on a case to case basis  <u>Other situations</u> : contraindicated	<u>Adult granulosa</u> : estrogens-containing contraceptions contraindicated	<u>Granulosa stage IA/B</u> : to be discussed on a case to case basis  <u>Other situations</u> : contraindicated
Rare epithelial tumours	Low-grade serous adenocarcinoma	Contraindicated	Not recommended	<u>Stage IA/B</u> : to be discussed on a case to case basis  <u>Stage &gt; IA/B</u> : contraindicated
	Endometrioid adenocarcinoma	Contraindicated	<u>High grade</u> : possible  <u>Low-grade</u> : not recommended	
	Mucinous adenocarcinoma	<u>Expansive</u> : to be discussed on a case to case basis <u>Infiltrative</u> : contraindicated	Possible	Possible
	Clear-cell adenocarcinoma	**	**	Possible

\*: High-risk histological criteria: micropapillary pattern, stromal microinvasion, peritoneal implants, mucinous borderline ovarian tumour with intraepithelial carcinoma

\*\* : These situations were not discussed as clear-cell adenocarcinoma treatment requires a radical surgery.