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Title: Fertility preservation in women with malignant and borderline ovarian tumors: experience of the French ESGO-certified center and pregnancy-associated cancer network (CALG)

Running title: Fertility preservation in ovarian tumors

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Abstract

Objective: To describe strategy and results of fertility preservation (FP) in patients with malignant and borderline ovarian tumors.

Methods: Consecutive cohort study of 43 women with malignant or borderline ovarian tumors who underwent FP between February 2013 and July 2019.

The study was conducted in national expert center in Tenon University Hospital, Sorbonne University: French ESGO-certified ovarian cancer center and pregnancy-associated cancer network (CALG). Main outcome measure was FP technique proposed by multidisciplinary committee, FP technique used, time after surgery, number of fragments, histology and follicle density (if ovarian tissue freezing), number of expected, retrieved and frozen oocytes (if ovarian stimulation).

Results: Pathological diagnosis was malignant epithelial ovarian tumor in five women (11.6%), rare malignant ovarian tumor in 14 (32.6%), borderline in 24 (55.8%), and mostly unilateral (79.1%) and stage I (76.7%). Mean age at diagnosis was 26.8 ± 6.9 years and mean tumor size 109.7 ± 61 mm. Before FP, mean AFC was 11.0 ± 6.1 and AMH levels were 2.7 ± 4.6 ng/ml. Six ovarian tissue-freezing procedures were performed (offered to 13). Twenty-four procedures of ovarian stimulation and oocyte freezing were performed after surgical treatment for 19 women (offered to 28) with a median interval of 188 days. The mean number of mature oocytes retrieved per stimulation was 12.4 ± 12.8 . At least 10 mature oocytes were frozen for 52.6% of the women. No FP was offered to five women.

Conclusion: Oocyte and ovarian tissue cryopreservation should be offered to patients with malignant and borderline ovarian tumors. More data are needed to confirm ovarian stimulation and ovarian tissue grafting safety.

Keywords: Fertility preservation; Rare malignant ovarian tumors; Borderline ovarian tumors; Oocyte freezing; Ovarian tissue freezing

1 **Introduction**

2 In 2017, the incidence of ovarian cancer in France was 7.1 for 100.000 women per year [1]
3 and the 5-year survival rate was 44% all stages included. Malignant epithelial ovarian tumors
4 (MEOT), mainly of serous histology, account for 60 to 75% of ovarian cancers [2]. While the mean
5 age at diagnosis is 65 years, 12.1% of MEOT occur before the age of 44 years with a 5-year
6 survival rate of 91.2% for stage IA and IB [3].

7 Rare malignant ovarian tumors (RMOT) occur more frequently in women of childbearing age
8 with a mean age at diagnosis between 18 and 30 years for germ cell tumors [4]. The incidence of
9 borderline ovarian tumors (BOT) is 2.5 to 5.5 per 100.000 [5]. Five- and 10-year overall survival
10 rates for early-stage BOT (Stage I) are 99% and 97%, respectively [6].

11 Surgical treatment recommended for early-stage BOT consists of cystectomy without
12 adjuvant therapy [7]. However, treatment for MOT mainly comprises salpingo-oophorectomy
13 followed by chemotherapy which impacts the ovarian reserve. Therefore, under French law, the
14 issue of fertility preservation (FP) should be raised in women diagnosed with MOT and
15 oocyte/ovarian tissue cryopreservation should be discussed [4,8].

16 As far as MEOT are concerned, evidence is currently too scarce to recommend ovarian tissue
17 freezing (OTF) for subsequent grafting. Similarly, the oncologic safety of ovarian stimulation using
18 pituitary gonadotropins after conservative surgery for stage IA MEOT is unknown [8].

19 Recent recommendations by the national network dedicated to rare gynecologic cancers based
20 on the DELPHI method [4] state that FP may be offered after individual risk/benefit balance
21 evaluation and multidisciplinary discussion. However, in this specific setting, few data are available
22 on FP.

23 Therefore, the present study aims to describe strategy and results of FP in patients with MOT
24 and BOT in a French expert centre.

25

26 **Materiel and method:**

27 Study setting and patients

28 This consecutive cohort study was conducted in a French ESGO-certified ovarian cancer
29 center and the pregnancy-associated cancer network (CALG) national expert center in Tenon
30 University Hospital, Sorbonne University. We retrospectively analyzed the prospective database of
31 patients undergoing FP consultation for ovarian tumors between February 2013 and July 2019.
32 Tumors were initially diagnosed between August 1995 and February 2019.

33 Procedures

34 *Patient information and fertility preservation decision making*

35 Patients received complete information about the various FP techniques available and were
36 counseled on a case-by-case basis after validation by a multidisciplinary committee composed of
37 ART specialists, embryologists, gynecologists and endocrinologists taking into account the advice
38 of the oncological committee. We noted whether patients received FP information “before surgical
39 treatment for ovarian tumor” or “after surgical treatment for ovarian tumor”.

40 The patients were informed that their anonymized personal data could be used for research
41 purposes according to French law including age at diagnosis, body mass index (BMI), smoking
42 status, gravidity and parity, tumor size, number and location (uni- or bilateral), presumed
43 preoperative histology, surgical procedure, and final histology. The data analysis protocol was
44 validated by the IRB (CEROG 2020-GYN-0301).

45

46 *Ovarian tissue freezing*

47 Ovarian tissue was harvested during laparoscopy or laparotomy and immediately transferred
48 to the laboratory at +4°C. Cortical tissue was isolated from the medulla and fragmented into pieces
49 of 5-10 x 5-10 mm². These specimens were subsequently frozen, as previously described [9] in
50 High Security Sterile Tubes (Cryo Bio System) containing cryoprotectants and 10% inactivated

51 patient serum. The dissection fluid was examined for cumulus-oocyte complexes (COCs) under a
52 stereomicroscope. After 24 hours of *in vitro* maturation (IVM) culture [10], the COCs were
53 denuded and mature metaphase II oocytes were frozen. For each patient, a fresh sample of medulla
54 and at least one fragment of cortex were processed for histologic analysis, including detection of
55 malignant cells and assessment of primordial follicle density.

56

57 *Mature oocyte freezing after ovarian stimulation*

58 Ovarian stimulation was performed postoperatively using gonadotropins. Stimulation
59 protocols were determined on an individual basis depending on evaluation of the ovarian reserve.
60 Our assisted reproduction technology (ART) unit routinely applies controlled ovarian
61 hyperstimulation (COHS) protocols. COHS was started either randomly or using the conventional
62 early follicular phase–start depending on the degree of emergency. Recombinant follicular
63 stimulating hormone (FSH) (GonalF Merck Serono France, Puregon MSD France, Elonva MSD
64 France or Bemfola Gedeon Richter France), recombinant FSH associated with luteinizing hormone
65 (LH) (Pergoveris Merck Serono France) or urinary gonadotropins (Menopur Ferring France) were
66 used in combination with gonadotropin-releasing hormone (GnRH) antagonist (Orgalutran Organon
67 France) from day 1 or 6 of FSH treatment to ovulation triggering day. Ovulation trigger was
68 programmed according to the number (>3) and size (>17 mm) of the follicles using human
69 chorionic gonadotropin (hCG) (Ovitrelle® Serono France) or GnRH agonist (Decapeptyl® Ipsen
70 France).

71

72 *Ovarian blockage using GnRH analogs*

73 Monthly injections of triptorelin 3mg (Decapeptyl® Ipsen France) were administered during
74 chemotherapy to preserve the ovarian reserve.

75

76 Outcome measures

77 We collected data on the ovarian reserve status (assessed by the antral follicle count (AFC)
78 and anti-Müllerian hormone (AMH) level), the FP technique proposed by the multidisciplinary
79 committee, the FP technique actually used, and the time after ovarian surgery that the technique was
80 performed. Data on the number of fragments and the histology and follicle density were collected if
81 OTF was performed. For women who underwent ovarian stimulation, information about the
82 protocol (agonist or antagonist, total gonadotropin dose, duration of stimulation, ovulation trigger
83 protocol), the expected number of oocytes, the number of retrieved and frozen oocytes were
84 collected.

85

86 Statistical analysis

87 Data were analyzed from the prospective database at Tenon Hospital. Population and tumor
88 characteristics, biologic and sonographic ovarian parameters, and number of mature oocytes
89 retrieved in borderline and malignant histology types were compared in a univariate analysis using
90 R software (R Core Team 2016). The student's t-test was used for quantitative parameters and the
91 χ^2 test for qualitative parameters. When event numbers were too small, Fischer's test was performed
92 instead of a χ^2 test. A p value under 0.05 denoted a significant difference.

93

94 **Results**

95

96 Epidemiologic and histologic characteristics of the population:

97 Two hundred and twenty patients with ovarian tumors referred to our center for FP
98 between February 2013 and July 2019 were included. Among the 220 patients, patients with
99 endometrioma, benign tumors, missing histology or non-surgical management were excluded.
100 Therefore, the study population was composed of 43 patients including 19 (44.2%)
101 preoperatively classified as benign (n=7) or undetermined (n=12) based on radiologic
102 findings. Among analyzed ovarian tumors BOT was present in 24 (55.8%) RMOT in 14 (32.6%)
103 and MEOT in 5 (11.6%) women. RMOT included both germ cell tumors (immature teratoma, yolk
104 sac tumor and embryonal carcinoma, dysgerminoma, embryonal carcinoma) and sex cord stroma
105 tumors (granulosa cell tumor).

106 Final histology was BOT in 24 patients (55.8%), RMOT in 14 (32.6%) and MEOT in five
107 (11.6%).

108 Twenty-one patients with MOT were treated in our center and 22 were referred for FP after
109 initial surgical treatment in a different center.

110 The characteristics of the population clustered by tumor type are detailed in Table I. The mean
111 age at diagnosis was 26.8 ± 6.9 years, mean BMI was 23.6 ± 5.3 kg/m², 11/41 had already been
112 pregnant, 4/41 had children, 56.2% had a partner, and 30.6% were smokers. Among the five
113 patients with MEOT, two were tested for BRCA mutation and were negative. Mean values of
114 ovarian reserve markers were AFC: 9.2 ± 5.4 follicles, and AMH: 2.30 ± 2.1 ng/ml before FP
115 (Table II). The mean age at the time of FP was 29.2 ± 6.1 years (Table II).

116

117 Tumor characteristics and surgical procedures

118 The mean tumor size was 109.7 ± 61 mm on imaging (MRI or ultrasonography). Tumors were
119 bilateral in 20.9% of the cases. The disease stages are detailed in Supplementary Table I. Nearly

120 half of the patients had stage IA. All the patients underwent uterus-sparing surgery. Three of the 34
121 women with unilateral tumors underwent conservative treatment. Four of the women with bilateral
122 tumors underwent a bilateral cystectomy, four underwent unilateral salpingo-oophorectomy and
123 contralateral cystectomy, and the last patient underwent bilateral salpingo-oophorectomy. Among
124 the patients with BOT, five were referred for FP after a recurrence (Supplementary Table I). One
125 patient with MEOT and one with RMOT consulted for stage III recurrence (Supplementary Table
126 I). Among the 12 patients who received chemotherapy, only one was treated before FP (Bleomycin
127 Etoposide Cisplatin for RMOT).

128
129 Fertility preservation:

130 The consultation for FP was preoperative for 27.9% of the women and took place at a median
131 of 27 days before the surgery (7-195 days). The remaining attended a postoperative FP consultation
132 at a median of 100 days after surgery (25-8348 days). The rate of preoperative FP consultations
133 increased during the study period from 0% in 2013 to 67% in 2019.

134
135 *Ovarian tissue freezing:*

136 OTF was offered to 13 women and performed in six (Table II). In 9 women it was proposed in
137 the association to ovarian stimulation. The proposition of OTF was based on the young age at
138 diagnosis (mean age of 23.9 ± 7.1 years) with low ovarian reserve (AMH level 1.27 ± 1.26 ng/mL)
139 and AFC 5.2 ± 3.7 follicles) limiting the chances of IVM or ovarian stimulation success. In 12
140 (92%) cases the existence of a contralateral lesion, the history of a previous ovarian surgery or post-
141 operative FP management was noted. One patient had bilateral endometriotic cysts associated with
142 1a stage BOT, for which a plasmajet was performed to avoid cystectomy.

143 The seven women for whom OTF was not performed included one patient without ovarian
144 cortex on histology, two patients treated by cystectomy instead of salpingo-oophorectomy, one with
145 a major reduction in ovarian reserve, and one who declined the procedure. OTF was canceled for

146 one woman due to technical issues and for one because final histology was stage IA serous
147 carcinoma.

148 Among the six women who undergone OTF the mean age was 25.8 ± 5.9 years and AMH
149 level 0.65 ± 0.56 ng/mL. In 2 cases, OTF was associated with ovarian stimulation but no oocyte
150 was cryopreserved. In 2 other cases, the analysis of the ovarian fragments allowed identification of
151 respectively 1 and 3 oocytes which underwent IVM and 1 and 2 oocytes were cryopreserved,
152 respectively. The OTF results are detailed in Table II. The median number of fragments was 22
153 ($14.75-28.50$) and median follicular density $0.045 /\text{mm}^2$ ($0.015-0.0925$). Ovarian cortex histology
154 was normal in all cases, except for one patient with glial tissue in an immature teratoma. No ovarian
155 tissue grafting has been performed to date.

156

157 *Mature oocyte freezing*

158 Mature oocyte freezing after ovarian stimulation was offered to 28 patients and 24
159 stimulations were performed for 19 patients. The proposition of ovarian stimulation was based on
160 the young age at diagnosis (mean age 25.9 ± 6.5 years) with preserved ovarian reserve (AMH level
161 2.37 ± 2.22 ng/mL and AFC 9.6 ± 5.3 follicles). In 18 cases (64%) there was no history of ovarian
162 surgery nor the presence of a contralateral lesion.

163 Among the nine patients who did not undergo ovarian stimulation, one stimulation was
164 cancelled because of MEOT recurrence after BOT surgery (Supplementary Table II, case 2), and
165 eight patients declined ovarian stimulation, including two patients with previous OTF. Stimulations
166 were performed postoperatively for all the patients except one with serous BOT recurrence. This
167 latter patient had previously been treated by unilateral salpingo-oophorectomy and contralateral
168 cystectomy and had undergone ovarian stimulation before surgical treatment of the recurrence.

169 The median time to stimulation after surgical treatment for the tumor was 188 days (34-8348).

170 The mean age of women in whom the ovarian stimulation was performed was 25.4 ± 7.3
171 years, the AMH level was $2.7 (1.45-3.7)$ ng/mL and AFC $12 (8.75-15.5)$ follicles. Among 10
172 women with MOT undergoing ovarian stimulation, FP was performed after chemotherapy in 1 case,
173 after radiotherapy in one woman and in one case after radioactive iodine therapy for ovarian
174 teratoma including malignant thyroid cells. In one patient no indication of complementary treatment
175 was retained. The remaining four FP were performed after surgical management of unilateral lesion.

176 Stimulation protocols and results are detailed in Table II. Ovarian stimulation protocols used
177 conventional early follicular phase–start in 79% of the cases, GnRH antagonists in 83.0%, and FSH
178 alone in 82.6%. The mean FSH dose was 3570 ± 1478 IU. Ovulation triggering was performed
179 using triptorelin in 95.4% of the stimulations.

180 The mean expected oocyte number per stimulation was 12.7 ± 8.9 and mean retrieved oocyte
181 per stimulation was 15.9 ± 17.3 . The mean mature frozen oocytes per stimulation was 12.3 ± 12.8 .

182 The mean number of stimulation cycles per patient was 1.26 ± 0.45 cycles. The mean number
183 of cumulated mature oocytes per patient was 16 ± 14.7 (n=17). Fewer than 5, at least 10, and at
184 least 15 mature oocytes were collected for 16.7%, 55.6% and 38.9 % of the patients, respectively.

185 No statistically significant difference was observed in terms of AFC and AMH between MOT
186 and BOT (Table II) nor between MEOT and RMOT (data not shown). Only one stimulation was
187 cancelled because of insufficient response. No clinical complications of controlled ovarian
188 hyperstimulation occurred.

189 For the five patients who requested embryo freezing, the mean number of frozen zygotes per
190 stimulation was 3.8 ± 1.2 .

191 One patient was offered ovarian puncture for IVM but she declined.

192
193 *Other fertility preservation procedures*

194 Ovarian blockage with GnRH analogs was offered and performed for two patients with stage
195 III MOT recurrence (one with MEOT and one RMOT) for whom chemotherapy started too quickly
196 for a cryopreservation strategy to be applied.

197 Follow-up was offered to one patient with serous BOT due to a good postoperative ovarian
198 reserve (AMH 4.5ng/ml).

199 No FP was offered to five patients: two of these had very low ovarian reserve markers (AMH
200 0 and 0.4 ng/ml, respectively); one had stage IC bilateral MOET with bilateral salpingo-
201 oophorectomy; one had a stage IIIC germ cell tumor treated with unilateral salpingo-oophorectomy
202 quickly followed by chemotherapy; and one had germ cell tumor with a contraindication to ovarian
203 stimulation as confirmed by the multidisciplinary committee.

204

205 Follow-up

206 Mean follow-up was 25.2 ± 29.7 months after FP (n=24) and 40.5 ± 52.9 months after surgery
207 (n=43). Among the patients with ovarian stimulation, the recurrence rate was 20% for BOT, 0% for
208 MEOT and RMOT. No recurrence was observed among the patients without ovarian stimulation.
209 One patient (Table III and Supplementary Table II: case 8) had two ovarian stimulations after
210 bilateral cystectomy for stage III BOT. The decision of ovarian stimulation and embryo
211 cryopreservation was decided on the basis of the young age and the excellent ovarian reserve (AMH
212 4.1 ng.ml). The first ovarian stimulation was performed 34 days after surgery, and the second 69
213 days after surgery followed by chemotherapy. Spontaneous pregnancy occurred 6 months after the
214 end of chemotherapy. Bilateral ovarian tumors of 3.5 cm and 2.5 cm were diagnosed during the
215 pregnancy. They were treated by bilateral salpingo-oophorectomy in the postpartum period
216 resulting in a diagnosis of stage IB bilateral BOT recurrence without microinvasion 19.7 months
217 after ovarian stimulation. Another patient (Supplementary Table II: case 3), had unilateral
218 cystectomy for stage IC1 serous BOT without invasion. A stage IC1 mucinous adenocarcinoma

219 recurrence was diagnosed during ovarian stimulation 6 months after surgery. None of the patients
220 died during follow-up.

221 Nine pregnancies (Table III) occurred during the follow-up: six spontaneously, two after
222 oocyte donation, and one after FP from a frozen embryo transfer. The pregnancies occurred from 6
223 to 50 months after surgery and resulted in four live births.

224

225

226 **Discussion**

227 Our study constitutes one of the two largest cohorts of fertility preservation for malignant
228 ovarian tumors [11]. Ovarian tissue freezing was performed in 6 women with the median number of
229 fragments of 22 (14.75-28.50) and the median follicular density of 0.045 /mm² (0.015-0.0925).
230 The mature oocyte vitrification after ovarian stimulation was performed in 17 women the mean
231 mature frozen oocyte number of 12.3 ± 12.8 per stimulation and the mean of 16 ± 14.7 cumulated
232 mature oocytes per patient. Ten or more frozen oocytes were obtained in 55.6% patients. We
233 observed an increase in preoperative fertility preservation consultations from 0% in 2013 to 67% in
234 2019 underlining the role of physicians involved in the management of malignant ovarian tumors.
235 The most striking data of the present study is the number of women with MOT and BOT who
236 decided proceed to oocyte cryopreservation with only 28.6% declining the procedure.

237 MOTs and BOTs are rare events in young women [3,8] and available evidence-based
238 medicine and recommendations for FP are limited [4,8].

239 Among the six women for whom OTF performed the mean age was 25.8 ± 5.9 years and
240 AMH level 0.6 (0.14-1.01) ng/mL. No primordial follicles were detected for one patient and
241 abnormal glial tissue was found in another. For the remaining four patients, follicular density was
242 very low (mean 0.06 primordial follicles per mm² (0.02-0.016)). The explanation of this low
243 follicular density could be associated to the criteria guiding the decision of OTF instead of IVM or

244 ovarian stimulation. This technique was proposed mainly to young women with low ovarian reserve
245 as the utilization of ovarian cortex is still limited. In patients with breast cancer, Sermondade et al
246 reported 1.3 primordial follicles per mm² [12]. In Fain-Kahn's study, OTF was only feasible in 53%
247 of the cases due to the absence of normal ovarian parenchyma [13]. For MOT, OTF is questionable
248 due to the risk of microscopic malignant cell clusters in a macroscopically normal cortex. In the
249 same manner, BOT cells have been identified in cryopreserved fragments from BOT patients [14].
250 This explains why OTF is rarely offered even if young patients could benefit from *ex vivo*
251 primordial follicle oocyte maturation in the future [15]. Moreover, BRCA somatic mutations may
252 be present in young patients with MEOT [16]. Although ovarian tissue grafting in a patient with
253 BRCA1 mutation has been reported [17], little is known about the long-term oncologic risk. In our
254 cohort of 43 women, OTF was proposed to 13 women (30%) but was performed only in six of them
255 (46%) mostly because of the absence of the cortex tissue during the surgical procedure. The
256 decision not to propose OTF to the 30 other women was based mainly on their age with weak
257 probability to develop *ex vivo* primordial follicle oocyte maturation before their 43 years, which is
258 the age limit for ART in France. On the other hand, OTF was not proposed to women with a very
259 good ovarian reserve (AMH > 3 ng/ml) as this procedure could alter the ovarian function in women
260 with rather good fertility prognosis after FSS and with a limited current use of the cortex.

261 After ovarian stimulation at least 10 and 15 frozen oocytes per patient were obtained in 41.7%
262 and 39.2% patients, respectively. The mean number of mature oocytes collected per stimulation for
263 patients with BOT, RMOT and MEOT were 12.0, 12.3 and 9.0, respectively. In agreement with our
264 results, previous studies have reported from 5 to 9.1 frozen oocytes retrieved in patients after FP for
265 ovarian cancer [11,18]. In the Von Wolf study [11], the mean total gonadotropin dose (2599 IU)
266 was lower than in the current study (3570 UI) which might explain their lower number of oocytes
267 while the mean age of the patients was similar. The recent literature review by the ESHRE task
268 force did not conclude that gonadotropin dose was correlated with retrieved oocyte numbers in poor

269 responders during ART [19]. The embryo cryopreservation in FP is rarely proposed in oncological
270 context and oocyte vitrification is rather privileged. In our cohort, zygote cryopreservation was only
271 performed in 3 women. As they presented a limited number of oocytes, few embryos were obtained
272 and a cryopreservation at zygote stage was chosen.

273 The FP was not proposed to two women because of the very low ovarian reserve (AMH 0.4
274 ng/ml and AFC 0 in a 36-year-old patient and AMH 0.03 ng/ml and AFC 2 in a 30 years-old
275 patient). The combination of age and ovarian reserve markers corresponded to very low chances of
276 pregnancy, and therefore the risk benefit balance was considered unfavorable. Reasonable live birth
277 rates have been reported when at least 8-10 metaphase II oocytes have been cryopreserved [20].

278 According to recent recommendations and French law, patients with fertility threatening
279 treatment should be informed about the possibility of FP prior to treatment initiation [21,22].
280 Therefore, once the option of fertility sparing surgery (FSS) has been taken, a complementary
281 cryopreservation strategy should be discussed. In this context, a preoperative FP consultation is
282 essential. In our study, only 25% of the FP consultations took place preoperatively. However, this
283 ratio increased from 0% in 2013 to 67% in 2019 underlining the role of physicians involved in the
284 management of MOT and BOT. The criteria for women being referred for FP consultation included
285 mainly young age and the parental project. However, this element could not be evaluated in our
286 study, as we do not have the access to the data concerning women to whom the FP was not
287 proposed. The 2010 guidelines underline the indication of FP consultation in women before all
288 treatments having a potential impact on gametogenesis. Thus a progressive modification in the FP
289 counselling has been observed. As recommended, to provide the best information concerning the FP
290 procedures, a systematic counselling should be proposed by physicians involved in the
291 management of MOT and BOT to all women in reproductive age before any treatment having the
292 potential impact on the ovarian function. To our knowledge, no data on pretreatment information

293 for MOT or BOT are available although Oktay et al. have shown that early information about FP
294 improved fertility outcomes in women with breast cancer [22].

295 Few data deal with the problem of renouncement of fertility preservation in women with
296 malignant and borderline ovarian tumors. In the context of endometriosis, Ferrier et al reported that
297 nearly 40% of patients enrolled in the FP process decided against the procedure just before ovarian
298 stimulation without the authors giving a clear reason why [23]. Women may highly value fertility
299 potential in spite of lack of safety data in this population. In addition in the present study, patients
300 were young (mean age 26.8 ± 6.9 years) and childless (median number of children before FP was 0
301 (0-0)). This may explain why the majority of referred women decided to follow the FP procedure.
302 As far as the decline of FP procedures is concerned, this decision could not be connected to the
303 costs of FP, as in France those treatments are covered by social security and no charge is required
304 from patients. Thus, the decision to forgo FP could be rather associated to the invasiveness and
305 constraints of FP procedures. The scarcity of data about the safety of FP procedures in BOT and
306 MOT could play a crucial role and in some women high chances of spontaneous pregnancy after
307 FSS might guide the decision.

308 Aside from information about disease prognosis, it is crucial to inform patients with MOT and
309 BOT about the specific risk of recurrence after ovarian stimulation. Our study underlines the low
310 risk of recurrence for patients with MEOT (one patient with stage 1A-1C1 presented recurrence 5
311 months after ovarian stimulation). However, the small sample population does not allow
312 underlining the low risk of recurrence for patients with MEOT. For stage IA MEOT, previous
313 studies have reported a contralateral recurrence rate of 6 % for grade 1 and 13% for grade 2 tumors
314 [21,24] while this risk reached 9% for IC grade 1 and 23% for IC grade 3 tumors [21] without
315 impacting overall survival [25,26]. For stage II-III MEOT, Petrillo et al found a recurrence and
316 death rate of 42.8% and 23.8%, respectively [27]. Low grade MEOT often express hormonal
317 receptors, potentially explaining the risk of recurrence after ovarian stimulation [28]. In our center

318 advanced stage MOT are not eligible to oocyte cryopreservation due to the risk associated to
319 ovarian puncture and malignant cells spillage. As far as MEOT are concerned, Fruscio et al. in their
320 retrospective multicenter study have reported that the grade 3 MEOT treated with fertility-sparing
321 surgery were associated with high rate of recurrence (HR 4.2, 95% CI: 1.5-11.7, P=0.0067) and
322 higher extra-ovarian relapse justifying the close follow-up [29]. The pregnancy rate in this
323 population of women wishing to conceive was 80% [29]. On the other hand, there is no evidence
324 that the radical surgery in patients with stage I MEOT could improve the oncological outcome of
325 those patients [30–32]. Our data provide more data to better inform patients about the risk of
326 recurrence after ovarian stimulation, that seems to be acceptable for early stages but remains a
327 matter of debate for advanced MEOT stages, especially expressing hormonal receptors.

328 For BOT, the main recurrence risk factors are the modalities of conservative surgery and the
329 initial staging [33]. In the present study, among the 19 patients with unilateral BOT, only two
330 recurrences occurred in patients who had a cystectomy. This observation is in line with literature
331 data reporting a ten-year recurrence rate for unilateral BOT treated with FSS by salpingo-
332 oophorectomy of 23% and 31% for cystectomy [34]. Among the five patients with bilateral serous
333 BOT, one of the three patients treated by unilateral salpingo-oophorectomy and contralateral
334 cystectomy and both patients treated by bilateral cystectomy experienced a recurrence. Delle
335 Marchette et al. have reported the recurrence rate of 62% and 72% in case of bilateral BOT treated
336 by salpingo-oophorectomy and cystectomy, respectively [34]. Recent French guidelines for BOT
337 treatment [4] state that uni- or bilateral cystectomy are recommended for serous BOT (the most
338 frequent histology). This is because of the high subsequent pregnancy rate and in spite of the higher
339 rate of recurrence as demonstrated in the only prospective trial on BOT conservative surgery [35].

340 No stimulating effects of FSH, estradiol [36] or hCG [37] have been observed *in vitro* in
341 BOT. However, in our study the invasive recurrence rate was 8.3% in contrast with previous studies

342 reporting a rate comprised between 0.6 and 3.7% [33,38–41]. This suggests that our patients may
343 have been under-staged initially especially those with peritoneal implants.

344 Several studies have shown a potential estrogenic sensitivity of granulosa cell tumors [42,43].
345 One of our patients with a granulosa tumor received ovarian stimulation without recurrence. The
346 priority in immature teratoma is to provide complete treatment to reduce the risk of recurrence [44].
347 In our study no recurrence occurred even though ovarian stimulation was performed before
348 chemotherapy in three of the four patients. As data on recurrence rates after FSS are scarce for
349 RMOT, decision making depends on histology and stage, and on a case by case basis. A
350 retrospective multicenter study analyzing the recurrence and long-term survival in 545 patients with
351 MEOT showed that fertility sparing surgery can be discussed in case of stage IA and IC grade 1 and
352 2 MEOT [45].

353 Another issue of the present study is that FP was frequently offered when recurrence was
354 diagnosed. This paradox can be explained by several factors. First, recurrences were mainly
355 observed in patients with initial BOT with a relatively high chance of spontaneous pregnancy but,
356 as demonstrated in the Palomba et al trial, relapse often occurs during the 2 postoperative years
357 [35]. These data justify both an early postoperative FP and a quick attempt at spontaneous
358 pregnancy without delay after initial surgery. The ovarian suppression by oral contraceptive pill
359 could be discussed in women treated for BOT, as the hormonal treatments could diminish the
360 recurrence risk [46]. However, this option is not appropriate for women willing to conceive rapidly.

361 In the present study, four live births occurred during follow-up after spontaneous pregnancy.
362 Few data about spontaneous pregnancy rates are available in patients with MOT according to
363 surgical management [47] and histologic type [48]. Around 67% of patients with early stage MEOT
364 have a spontaneous pregnancy [26,49–53] and Fauvet et al. reported that 67.4% of patients with
365 BOT were pregnant after FSS [6]. Moreover, Palomba et al. showed an overall pregnancy rate of

366 93.3% after FSS and ART [47]. After FSS for granulosa cell [54] and germ cell tumors [55]
367 spontaneous pregnancy rates of 86.4% and 93%, respectively, have been reported.

368 Some limits of the present study deserve to be underlined. First, the retrospective nature
369 cannot avoid all biases. Second, the small sample size of the study population, and especially of
370 patients with MEOT and RMOT, limits a comprehensive evaluation of safety of the FP technique.
371 Finally, a longer follow-up is necessary to better evaluate the long-term oncologic risk associated
372 with FP as well as pregnancy outcomes.

373

374 **Conclusion**

375 In conclusion, despite some limits of the present study, our data confirm that FP consultation should
376 be systematically discussed with women of childbearing age with MOT and included in the
377 oncologic management since satisfactory oocyte retrieval results are obtained in more than 50% of
378 patients. Other FP options can be discussed and rather good fertility outcomes are observed.
379 Improvements in the *ex vivo* primordial follicle maturation process could, in the future, constitute an
380 alternative to classic FP techniques without exposing the patient to the risks associated with ovarian
381 stimulation or ovarian tissue grafting. In the meantime, long-term studies on FP techniques are
382 needed to appropriately counsel patients on their fertility management in ovarian tumors.

383

384 **Author's roles**

385 EdK, ITN, ED, NCB and KK were involved in conception and design, SG, AL, NS and JV were
386 involved in acquisition of data and SG, AL, EdK, NS, JV, ITN, SB, ED, NCB and KK were
387 involved in data analysis and interpretation. All authors were involved in drafting the article and all

388 authors were involved in revising the manuscript critically for important intellectual content. All
389 authors have given the final approval of the version to be published.

390

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394

395 **Conflict of interest**

396 Authors declare that they have no conflict of interest to declare.

397

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Table I. Characteristics of the 43 patients referred for FP

| Histology | Malignant Epithelial Ovarian Tumours and Rare Malignant Ovarian Tumours | Borderline Ovarian Tumours | All tumours | <i>p</i> |
|--|--|-----------------------------------|--------------------|-----------------|
| Number | 19 | 24 | 43 | |
| Age at diagnosis (mean ± SD, years) | 26.1 ± 7.2 | 27.8 ± 6.5 | 26.8 ± 6.9 | 0.44 |
| BMI (mean ± SD, kg/m ²) | 22.9 ± 4.7 | 24.2 ± 5.9 | 23.6 ± 5.3 | 0.46 |
| Women with previous pregnancies (x/n) | 4/17 | 7/24 | 11/41 | 0.69 |
| Women with previous live birth (x/n) | 2/17 | 2/24 | 4/41 | 0.72 |
| Women with a partner (x/n) | 7/14 | 11/18 | 18/32 | 0.53 |
| Declared tobacco smoking (x/n) | 2/15 | 9/21 | 11/36 | 0.06 |
| Fertility preservation consultation preoperative (x (%)) | 3 (15.8) | 8 (33.3) | 11 (25.6) | 0.19 |
| AFC (mean ± SD, mm) | 9.0 ± 4.6 | 13.6 ± 7.1 | 11.0 ± 6.1 | 0.054 |
| AMH (mean ± SD, ng/mL) | 1.6 ± 1.4 | 3.7 ± 5.9 | 2.7 ± 4.6 | 0.24 |
| Bilateral lesions (x (%)) | 2 (10.5) | 7 (29.2) | 9 (20.9) | 0.14 |
| Radiological ovarian tumour size* (mean ± SD, mm) | 142.4 ± 72.6 | 91 ± 47 | 109.7 ± 61 | 0.03 |

* as evaluated on MRI or US scan

BMI: Body Mass Index; AFC: Antral Follicle Count; AMH: Anti Mullerian Hormone, SD: Standard Deviation

x: event number; n: total patients or lesions number

Table II. Fertility preservation techniques

| Histology | Malignant Epithelial Ovarian Tumours and Rare Malignant Ovarian Tumours | Borderline Ovarian Tumours | p |
|--|--|-----------------------------------|----------|
| Number | 19 | 24 | |
| AMH before FP (mean ± SD, ng/ml) | 2.1 ± 1.3 | 2.4 ± 2.5 | 0.75 |
| AFC before FP (mean ± SD) | 10.0 ± 5.0 | 7.6 ± 5.9 | 0.37 |
| Age at FP (mean ± SD, years) | 28.4 ± 4.3 | 29.4 ± 6.4 | 0.70 |
| OVARIAN TISSU FREEZING | | | |
| Ovarian tissue freezing offered/performed | 4/2 | 9/4 | - |
| Fragment number (median (IQR)) | 5.5 (0.0-11.0) | 22.0 (4.0-29.5) | 0.33 |
| Fragments follicular density (median (IQR), primordial follicles/mm ²) | 0.08 (0.00-0.16) | 0.05 (0.02-0.07) | 1 |
| MATURE OOCYTES FREEZING AFTER OVARIAN STIMULATION | | | |
| Mature oocytes freezing offered/performed | 11/9 | 17/10 | - |
| Number of cycles | 9 | 15 | - |
| Average time after surgery (mean ± SD, days) | 1694 ± 2718 | 199 ± 153 | 0.10 |
| Antagonist protocol (x(%)) | 7 (78) | 13 (87) | 0.57 |
| Random start protocol (x(%)) | 3 (33.3) | 2 (13) | 0.24 |
| Total gonadotrophine dose (mean ± SD, IU) | 4131 ± 903 | 3272 ± 1659 | 0.19 |
| Stimulation duration (mean ± SD, days) | 11.4 ± 2.3 | 10.5 ± 2.2 | 0.36 |
| Expected oocytes (mean ± SD) | 11.4 ± 10.3 | 13.4 ± 8.3 | 0.62 |
| Collected oocytes per stimulation (mean ± SD) | 15.9 ± 11.3 | 16.0 ± 19.9 | 0.99 |
| Mature oocytes per stimulation (mean ± SD) | 13.1 ± 10.5 | 12.0 ± 14.1 | 0.85 |
| Mature oocytes per stimulation (%) | | | |
| <5 | 25 | 26.7 | |
| 5-9 | 25 | 26.7 | 1 |
| 10-14 | 12.5 | 13.3 | |
| 15 | 37.5 | 33.3 | |
| Cumulated mature oocytes per patient (%) | | | |
| <5 | 25 | 10 | |
| 5-9 | 25 | 30 | 0.85 |
| 10-14 | 12.5 | 20 | |
| > 15 | 37.5 | 40 | |

AFC: Antral Follicle Count, AMH: Anti Mullerian Hormone, FP: fertility preservation, NA: Non Appropriate, SD: Standard Deviation

x : event number

Table III. Pregnancies after malignant ovarian tumor

| Case | Pregnancy onset | Pregnancy outcome | Tumour type and stage | Oncological treatment | Delay after surgery (month) |
|--------|--------------------------------|----------------------------------|------------------------|-----------------------|-----------------------------|
| 8 | Spontaneous | Live birth | Serous BOT, stage III | BC + Chemotherapy | 13 |
| 10 | Spontaneous | Miscarriage | Mucinous BOT, stage IA | US | 23 |
| 11 | Spontaneous | Miscarriage | Serous BOT, stage IA | UC | 24 |
| 11 bis | Spontaneous | Miscarriage | Serous BOT, stage IA | UC | 32 |
| 12 | Spontaneous | Live birth | RMOT, stage IC1 | US + Chemotherapy | 18 |
| 13 | Spontaneous | Pregnancy in progress (8 months) | RMOT, stage NA | US + Iratherapy | 23 |
| 14 | Egg donation | Live birth | Serous BOT, stage IC3 | US + CC | 52 |
| 15 | Egg donation | Miscarriage | MEOT, stage IC1 | US | 49 |
| 16 | Frozen embryo tranfer after FP | Live birth | Serous MEOT, stage IA | US | NA |

ART: Assisted Reproductive Technology; FP: Fertility Preservation; US: Unilateral Salpingo-oophorectomy; UC: Unilateral Cystectomy; BC: Bilateral Cystectomy; CC: Controlateral Cystectomy; NA: Not Available