Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2010;70:160–165
DOI: 10.1159/000316264

Received: November 30, 2009
Accepted: February 20, 2010
Published online: June 16, 2010

Clinical Recommendation on Fertility Preservation in Borderline Ovarian Neoplasm: Ovarian Stimulation and Oocyte Retrieval after Conservative Surgery

Dominik Denschlag Michael von Wolff Frederic Amant Vesna Kesic
Nicholas Reed Achim Schneider Alexandros Rodolakis

Task Force Fertility Preservation, European Society of Gynecologic Oncology, European Society of Human Reproduction and Embryology, and Department of Obstetrics and Gynecology, University of Freiburg School of Medicine, Freiburg, Germany

Key Words
Tumor, borderline · Neoplasm, ovarian · Ovarian stimulation · Oocyte retrieval

Abstract
Aim: To evaluate safety and fertility outcome after assisted conception in patients who were treated conservatively for a borderline ovarian tumor (BOT). ***Methods:*** A systematic literature review using Medline was conducted. From all the relevant case series the following information was obtained for each reported patient: primary diagnosis; disease stage; surgical treatment; duration of follow-up; incidence of recurrence; current disease status; the number of controlled ovarian stimulation cycles and/or oocyte retrievals, and successful pregnancies. ***Results:*** Overall 588 articles were screened, of which finally 15 reports including 62 patients met the inclusion criteria. Within a median follow-up duration of 52 months in this small group of patients, overall 12 patients (19.4%) had recurrences, and those recurrences were again successfully treated by surgery in 11 patients. In terms of assisted reproductive outcome, in our series overall 152 ovarian stimulation cycles as well as 135 oocyte retrievals were performed with a baby-take-home rate of 28.3% per stimulated cycle. ***Conclusion:*** It is mandatory to counsel all patients with a history of BOT who are seeking treatment for infertility that, due to the limited data, it is unclear whether assisted reproductive techniques are associated with an increased risk of recurrence.

Introduction

Borderline ovarian tumors (BOTs), also called atypically proliferating tumors and/or low malignant potential tumors, form a separate entity within the group of ovarian tumors. These tumors are characterized by a certain degree of cellular proliferation and nuclear atypia in the absence of infiltrative destructive growth or obvious stromal invasion. BOTs account for 10–20% of ovarian epithelial tumors [1].

In comparison to invasive carcinomas, BOTs are mostly diagnosed at an earlier stage, resulting in an excel-

D.D., F.A., V.K., N.R., A.S. and A.R. are members of the ESGO Task Force Fertility Preservation, and M.v.W is a member of the ESHRE Task Force Fertility Preservation.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–7346/10/0703–0160$26.00/0

Accessible online at:
www.karger.com/goi

Dominik Denschlag, MD
Department of Obstetrics and Gynecology, University of Freiburg School of Medicine
Hugstetter Strasse 55, DE–79106 Freiburg (Germany)
Tel. +49 761 270 3002, Fax +49 761 270 2932
E-Mail dominik.denschlag@uniklinik-freiburg.de

lent prognosis. In a series of 2,818 women with BOTs from the Surveillance, Epidemiology, and End Results (SEER) database, the National Cancer Institute reported the following 5- and 10-year relative survival rates [2]: stage I, 99 and 97%; stage II, 98 and 90%; stage III, 96 and 88%, and stage IV, 77 and 69%.

The average age at diagnosis is in the mid 40s, but the highest frequency relative to invasive ovarian cancer of these tumors occurs in the 15- to 29-year-old age group. Thus, the disease frequently affects women who wish to retain their fertility.

Whereas in the past total abdominal hysterectomy, bilateral salpingo-oophorectomy with staging, was the standard treatment regardless of age, unilateral salpingo-oophorectomy and staging with preservation of the uterus and contralateral ovary has become the recommended management for women who desire to bear a child [3]. Published series have shown recurrence rates of approximately 10–30% among women treated with such conservative surgery, with the vast majority of recurrences occurring as a second borderline tumor [4, 5].

Infertility is frequently observed in patients with BOTs, with 10–35% of patients already having a history of infertility before treatment [5, 6]. Because surgery itself can cause infertility as a sequel of adhesions and removal of the ovary and fallopian tube, the question of whether these patients can have fertility treatment, e.g. in the form of in vitro fertilization, is frequently asked.

The management of such patients has been a controversial task, particularly since the use of fertility drugs was identified as a risk factor for the development of ovarian neoplasms in some studies [7, 8]; however, other studies have not been able to confirm this association [9, 10]. A meta-analysis of all the available literature found that infertility treatment did not independently increase the risk of ovarian neoplasm; however, infertility itself was an independent risk factor for this disorder [11]. Thus, the apparent association between fertility drug use and epithelial ovarian neoplasm appears to be related to the fact that these drugs are more likely to be used in infertile women.

In addition, it is of note that data from in vitro experimental approaches regarding the effects of gonadotropins on the growth of ovarian epithelial cells have been conflicting [12, 13].

In light of these conflicting reports, the question has been raised whether assisted reproductive techniques, including controlled ovarian stimulation and/or transvaginal oocyte retrieval, can be safely offered to patients after conservative surgery for BOTs.

Material and Methods

Eligible case series and reports were identified using PubMed software to search Medline (US National Library of Medicine, Bethesda, Md., USA) for relevant articles from 1978 to September 2008, and by hand-searching the reference lists of the retrieved articles. For computer searches, we used the following MeSH terms or text words: 'infertility', 'ovarian hyper-stimulation', or 'oocyte retrieval', combined with 'ovarian cancer', 'borderline', or 'low malignant potential'. The search was limited to reports published in English.

We read the abstracts of all identified publications to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the inclusion criteria. Where multiple reports from one study were found, the most recent or most complete publication was used. Publications were included in this summary if they report sufficiently on the outcome of patients who underwent controlled ovarian stimulation and/or transvaginal oocyte retrieval after conservative surgery for BOTs. Since our focus was recurrent and not primary disease, we only included patients who underwent assisted reproductive techniques after conservative surgery for ovarian borderline tumors, regardless of whether the patient had an in vitro fertilization procedure prior to the primary diagnosis or not, since in our opinion this has no impact on recurrent disease. The few patients who already had recurrent disease prior to assisted conception where successfully salvaged with no evidence of a second recurrence and were therefore also included. Publications considered sufficient had to report at least the number of patients, incidence of recurrences, current disease status, duration of follow-up, number of ovarian stimulation cycles, number of oocyte retrievals, and number of successful pregnancies. Conservative surgery was defined as a surgical procedure which did not result in the complete removal of both ovaries. A complete surgical staging procedure included exploration of the entire abdominal cavity with peritoneal washings, infracolic omentectomy, and multiple peritoneal biopsies. Since the time between assisted reproductive intervention and recurrent disease was not clearly stated in the majority of the cases, we defined the time until recurrent disease beginning from the date of conservative surgery.

The following information was recorded for each reported patient: primary diagnosis; initial disease stage; histologic subtype; surgical treatment; duration of follow-up; incidence of recurrence; current disease status; number of controlled ovarian stimulation cycles and/or oocyte retrievals, and successful pregnancies.

These data are summarized in a descriptive manner. Continuous variables are reported as median ± standard deviation (unless otherwise specified). Categorical variables are reported as absolute number of patients and/or percentages of the whole group studied.

Results

Overall 588 articles were screened, of which finally 15 reports including 62 patients met the inclusion criteria, and therefore were considered as the study group. Those articles are listed in table 1.

Table 1. Reports on patients with a previous history of borderline ovarian tumor who underwent ovarian hyperstimulation (OS) and/or oocyte retrieval (OR) for assisted conception

Author	Patients	Recurrences	Deaths	Duration of FU months	OS	OR	Pregnancies
Nijman et al. [21], 1992	1	1	0	15	2	2	1
Mantzavinos et al. [22], 1994	2	0	0	60	3	3	1
Hershkovitz et al. [23], 1998	1	0	0	48	2	2	1
Hoffman et al. [24], 1999	1	0	0	53	3	2	1
Gallot et al. [25], 2000	1	0	0	41	1	1	1
Beiner et al. [26], 2001	7	2	0	50	18	18	6
Camatte et al. [27], 2002	2	2	0	81	2	1	2
Steinkampf et al. [28], 2003	2	0	0	108	11	4	2
Chan et al. [29], 2003	1	0	0	80	1	1	1
Fasouliotis et al. [30], 2004	5	1	0	39	17	17	6
Attar et al. [15], 2004	1	1	0	18	1	1	1
Marcickiewicz et al. [31], 2006	2	0	0	97	2	2	2
Fortin et al. [16], 2007	30	4	0	42	78	70	13
Park et al. [14], 2007	5	0	0	30	10	10	4
Porcu et al. [32], 2008	1	1	0	81	1	1	1
Total	62	12	0	52 ± 27[a]	152	135	43

FU = Follow-up.
[a] Median ± standard deviation.

The baseline characteristics and outcome of the identified patients who underwent assisted conception after conservative surgery for ovarian borderline tumor are listed in table 2.

Except for 1 [14] patient who was treated with 6 cycles of paclitaxel and carboplatin for micro-invasive disease, none of the patients received adjuvant chemotherapy or radiation following initial surgery.

Within a median follow-up duration of 52 months, overall 12 patients (19.4%) in the study group had recurrences after assisted reproductive techniques. Of these 12 patients, 11 had a second borderline recurrence which was successfully treated by surgery. All of these 11 patients were free of disease at the time reported. In 1 patient, who was initially diagnosed with a stage III serous BOT showing micropapillary features, the disease reoccurred as a malignant tumor requiring adjuvant chemotherapy [15]. The initial baseline characteristics of those patients who were diagnosed with recurrent disease are listed separately in table 3.

In terms of assisted reproductive techniques after surgery, overall 152 ovarian stimulation cycles as well as 135 oocyte retrievals were performed with a baby-take-home rate of 28.3% per stimulated cycle.

Comments

This summary of case series reports on the outcome of 62 patients assembled from 15 publications on patients with BOTs who underwent gonadotropin stimulation with or without oocyte retrieval after fertility-sparing cancer treatment.

Our main goal was to address the question whether assisted reproductive techniques can be safely offered to patients after conservative surgery for BOTs.

In the so far largest case series reported, Fortin et al. [16] describe altogether 4 recurrences in 30 patients overall after a median follow-up of 93 months (13.3%), therefore suggesting that assisted reproductive techniques could be used safely in patients who experience infertility after conservative management of BOTs [16].

Together with other reports, we calculated a higher recurrence rate of overall 19.4% which questions the safety of assisted reproductive techniques in these patients.

This recurrence rate is especially worrisome in light of the so far largest population-based analysis of long-term outcomes following conservative surgery for BOTs including 193 patients [17], which reported an overall recurrence rate of only 10.9%.

Table 2. Baseline characteristics and outcome in patients who underwent assisted conception after conservative surgery for ovarian borderline tumor

	Patients (n = 62)
Histology	
Serous	41 (66%)
Mucinous	14 (22%)
Other	1 (2%)
Not stated	6 (10%)
Disease stage	
I	42 (68%)
II	4 (6%)
III	14 (23%)
IV	0
Not stated	2 (3%)
Staging procedure	
Complete	54 (87%)
Unstaged/incomplete	8 (13%)
Surgical procedure	
Cystectomy	16 (26%)
USO	43 (69%)
Other	0
Not stated	3 (5%)
Median follow-up, months	52
Recurrence	12 (19.4%)

USO = Unilateral salpingo-oophorectomy.

Table 3. Baseline characteristics of patients who were diagnosed with recurrent disease in the study group

Author	Histology	Disease stage	Surgical procedure
Nijman et al. [21], 1992	Serous	III	USO
Beiner et al. [26], 2001	Mucinous	Not staged	USO
	Serous	III	USO
Camatte et al. [27], 2002	Not stated	III	Cystectomy
	Not stated	III	USO
Fasouliotis et al. [30], 2004	Serous	I	Cystectomy
Attar et al. [15], 2004	Serous (micro-papillary)	III	USO
Fortin et al. [16], 2007	Serous	I	Cystectomy
	Serous	I	USO
	Serous	I	USO
	Serous	III	USO
Porcu et al. [32], 2008	Serous	I	USO

USO = Unilateral salpingo-oophorectomy.

It is unclear if this lower recurrence rate is related to a lower rate of advanced disease (stage II and III) in the series of Suh-Burgmann [17] in comparison to ours (3 vs. 29%). However, the stage distribution in her series is limited by the fact that only 8% of the patients had been completely staged in contrast to 87% of the patients included in our series.

According to the stage distribution in the general population, advanced disease (stage II, III, and IV) occurs in up to 20% of the patients [18]. Therefore, one might speculate that the high rate of stage I disease in the series published by Suh-Burgmann [17] (97%) is most likely caused by the fact that the vast majority of patients did not undergo a complete surgical staging procedure, which might have revealed more advanced disease.

According to a French multicenter study, 15% of the patients with initially incomplete staging who underwent a second surgical procedure were upstaged according to final pathology [19]. However, in comparison to a non-staged control group the rate of recurrence did not differ. Therefore, we can only speculate about the natural behavior of these 'silent' borderline tumor cells which are left in situ in not-staged patients and do not lead to a higher rate of recurrence. Moreover, even in the case these cells would continue to grow, the fact that in our series the rate of recurrence is higher compared to the series reported by Suh-Burgmann [17] makes assisted conception even more worrisome.

On the contrary, if including only patients with stage I disease as proposed by several experts [3], one might argue that according to our data assisted reproductive techniques could be performed safely since the rate of recurrence in this subgroup (11.9%; n = 5 out of 42 patients with stage I disease) does not significantly differ from the recurrence rate reported by Suh-Burgmann [17] in her analysis.

According to our analysis, the higher rate of recurrence for all patients in our series does not seem to be related to the type of initial surgery since the incidence of cystectomy versus total oophorectomy is comparable to the series published by Suh-Burgmann [17] (26 vs. 24%). Based on the available literature, the rate of recurrence is increased after cystectomy (between 12 and 58%) compared to conventional oophorectomy [3, 4]. This higher rate of relapse implies that the optimal treatment of BOT is to perform a unilateral oophorectomy. A cystectomy should only be performed in cases with bilateral tumor and/or in patients with only one ovary remaining (previous history of an oophorectomy).

Nevertheless, a direct statistical comparison of our data to a historic control is inappropriate since the majority of the data is based on cumulative case series in which the individual data of the patients were not provided. Thus, a multivariate analysis controlling for possible confounders such as patient age is not feasible. Moreover, unfortunately in the series published by Suh-Burgmann [17] no comment was made on whether any of the patients included had also received infertility treatment.

It is of note that despite the relatively high recurrence rate in patients who underwent controlled ovarian stimulation and/or oocyte retrieval, the overall outcome in terms of survival is still excellent (100% after a median follow-up of 52 months), with 98.4% of the patients being free of disease at the time reported. These data further support the already existing evidence about the fairly good prognosis of ovarian borderline tumors even in case of recurrent disease [20].

With respect to the time to recurrence, about two thirds of the patients who did recur were diagnosed within 5 years after the initial surgery. For example, according to Suh-Burgmann [17], the median time to recurrence was 4.7 years, with 5 (23%) recurrences between 0 and 2 years following surgery, 8 (38%) recurrences between 2 and 5 years, 6 (28%) between 5 and 10 years, and 2 (10%) more than 10 years after initial surgery.

In conclusion, according to the limited data, it is mandatory to counsel all patients with a history of BOT, who are seeking treatment for infertility, that it is unclear whether assisted reproductive techniques are associated with an increased risk of recurrence.

Moreover, since patients with this diagnosis are rare and/or probably underreported, we propose a centralized web-based reporting system in order to collect more data regarding the outcome after assisted reproductive techniques in patients with a history of BOTs.

References

1 Pecorelli S, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO annual report on the results of treatment in gynaecological cancer. J Epidemiol Biostat 1998;3:75–102.
2 Trimble CL, Kosary C, Trimble EL: Long-term survival and patterns of care in women with ovarian tumors of low malignant potential. Gynecol Oncol 2002;86:34–37.
3 Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I: Management of borderline ovarian neoplasms. J Clin Oncol 2007; 25:2928–2937.
4 Morice P: Borderline tumours of the ovary and fertility. Eur J Cancer 2006;42:149–158.
5 Fauvet R, Poncelet C, Boccara J, Descamps P, Fondrinier E, Daraï E: Fertility after conservative treatment for borderline ovarian tumors: a French multicenter study. Fertil Steril 2005;83:284–290; quiz 525–526.
6 Gotlieb WH, Flikker S, Davidson B, Korach Y, Kopolovic J, Ben-Baruch G: Borderline tumors of the ovary: fertility treatment, conservative management, and pregnancy outcome. Cancer 1998;82:141–146.
7 Parazzini F, Negri E, La Vecchia C, et al: Treatment for fertility and risk of ovarian tumors of borderline malignancy. Gynecol Oncol 1998;68:226–228.
8 Shushan A, Paltiel O, Schenker JG: Induction of ovulation and borderline ovarian cancer – the hormonal connection? Eur J Obstet Gynecol Reprod Biol 1999;85:71–74.
9 Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN: Ovarian stimulation and borderline ovarian tumors: a case-control study. Fertil Steril 1998;70:1049–1055.
10 Cusido M, Fabregas R, Pere BS, Escayola C, Barri PN: Ovulation induction treatment and risk of borderline ovarian tumors. Gynecol Endocrinol 2007;23:373–376.
11 Kashyap S, Moher D, Fung MF, Rosenwaks Z: Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. Obstet Gynecol 2004;103:785–794.
12 Zheng W, Lu JJ, Luo F, et al: Ovarian epithelial tumor growth promotion by follicle-stimulating hormone and inhibition of the effect by luteinizing hormone. Gynecol Oncol 2000;76:80–88.
13 Tourgeman DE, Lu JJ, Boostanfar R, Amezcua C, Felix JC, Paulson RJ: Human chorionic gonadotropin suppresses ovarian epithelial neoplastic cell proliferation in vitro. Fertil Steril 2002;78:1096–1099.
14 Park CW, Yang KM, Kim HO, et al: Outcomes of controlled ovarian hyperstimulation/in vitro fertilization for infertile patients with borderline ovarian tumor after conservative treatment. J Korean Med Sci 2007;22(suppl):S134–S138.
15 Attar E, Berkman S, Topuz S, Baysal B, Akhan S, Chambers JT: Evolutive peritoneal disease after conservative management and the use of infertility drugs in a patient with stage IIIC borderline micro-papillary serous carcinoma (MPSC) of the ovary: case report. Hum Reprod 2004;19:1472–1475.
16 Fortin A, Morice P, Thoury A, Camatte S, Dhainaut C, Madelenat P: Impact of infertility drugs after treatment of borderline ovarian tumors: results of a retrospective multicenter study. Fertil Steril 2007;87:591–596.
17 Suh-Burgmann E: Long-term outcomes following conservative surgery for borderline tumor of the ovary: a large population-based study. Gynecol Oncol 2006;103:841–847.
18 Heintz AP, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. J Epidemiol Biostat 2001;6:107–138.
19 Fauvet R, Boccara J, Dufournet C, David-Montefiore E, Poncelet C, Daraï E: Restaging surgery for women with borderline ovarian tumors: results of a French multicenter study. Cancer 2004;100:1145–1151.
20 Zanetta G, Rota S, Chiari S, Bonazzi C, Bratina G, Mangioni C: Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. J Clin Oncol 2001;19:2658–2664.
21 Nijman HW, Burger CW, Baak JP, Schats R, Vermorken JB, Kenemans P: Borderline malignancy of the ovary and controlled hyperstimulation, a report of 2 cases. Eur J Cancer 1992;28A:1971–1973.
22 Mantzavinos T, Kanakas N, Genatas C, Papadias K, Zourlas PA: Five years' follow-up in two patients with borderline tumours of the ovary hyperstimulated by gonadotrophin therapy for in-vitro fertilization. Human Reprod 1994;9:2032–2033.
23 Hershkovitz R, Lunenfeld E, Piura B, et al: Ovulation induction in three infertile patients with ovarian borderline tumor. Israel J Obstet Gynecol 1998;9:271–275.

24 Hoffman JS, Laird L, Benadiva C, Dreiss R: In vitro fertilization following conservative management of stage 3 serous borderline tumor of the ovary. Gynecol Oncol 1999;74:515–518.
25 Gallot D, Pouly JL, Janny L, et al: Successful transfer of frozen-thawed embryos obtained immediately before radical surgery for stage IIIa serous borderline ovarian tumour: case report. Hum Reprod 2000;15:2347–2350.
26 Beiner ME, Gotlieb WH, Davidson B, Kopolovic J, Ben-Baruch G: Infertility treatment after conservative management of borderline ovarian tumors. Cancer 2001;92:320–325.
27 Camatte S, Morice P, Pautier P, Atallah D, Duvillard P, Castaigne D: Fertility results after conservative treatment of advanced stage serous borderline tumour of the ovary. BJOG 2002;109:376–380.
28 Steinkampf MP, Dharia SP, Hammond K: Assisted reproduction in patients with early-stage ovarian malignancies. Fertil Steril 2003;80:1510–1512.
29 Chan JK, Lin YG, Loizzi V, Ghobriel M, Di-Saia PJ, Berman ML: Borderline ovarian tumors in reproductive-age women. Fertility-sparing surgery and outcome. J Reprod Med 2003;48:756–760.
30 Fasouliotis SJ, Davis O, Schattman G, Spandorfer SD, Kligman I, Rosenwaks Z: Safety and efficacy of infertility treatment after conservative management of borderline ovarian tumors: a preliminary report. Fertil Steril 2004;82:568–572.
31 Marcickiewicz J, Brannstrom M: Fertility preserving surgical treatment of borderline ovarian tumour: long-term consequence for fertility and recurrence. Acta Obstet Gynecol Scand 2006;85:1496–1500.
32 Porcu E, Venturoli S, Damiano G, et al: Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod Biomed Online 2008;17:265–267.