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Review

Borderline tumours of the ovary and fertility

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ABSTRACT

Standard management of borderline ovarian tumours (BOT) is historically radical and based on hysterectomy, bilateral salpingo-oophorectomy and peritoneal staging. But, as 1/3 of BOTs are diagnosed in patients aged less than 40 years, treatments preserving fertility-potential (with preservation of the uterus and at least part of one ovary) has seen great developments in the last decade. Such treatments increase the rate of recurrences (between 15% and 35% depending on the type of conservative surgery), but without any impact on patient survival as most recurrent diseases are of the borderline type, easily curable and with excellent prognosis. The spontaneous pregnancy rate is nearly 50%. In case of persistent infertility, it seems that the use of ovarian induction or in vitro fertilization procedures could be proposed in selected cases. Follow-up is essential and based on clinical examination and routine ultrasonography. The interest of completion surgery (removal of the retained ovary) in patients who obtained pregnancy remains debated. In conclusion, conservative management of at least part of one ovary and uterus could be safely proposed at least to patients with early stage BOT, in order to preserve fertility-potential. The rate of recurrence is increased but without any impact on survival.

Borderline tumour of the ovary (BOT) was described for the first time in 1929 by Taylor [1]. It represents 10–20% of epithelial ovarian tumours with an incidence evaluated to 4.8/10000 cases per year [2]. This incidence increases up to the sixth decade, then stable between the sixth and eighth decade and decreases after the eighth decade [3]. The mean age of diagnosis of BOT is 10 years earlier than that of epithelial ovarian cancer. Nearly one-third of BOTs were diagnosed in patients aged under 40, that is in a group of patients where fertility preserving treatments should be considered [4].

For over 50 years, BOTs was considered in the natural history of ovarian cancer as a premalignant disease. The treatment of this tumour, as in malignant ovarian diseases, was based on radical surgery (hysterectomy with bilateral salpingo-oophorectomy) to reduce the risk of recurrence in the form of invasive carcinoma. But over these last two decades, as the prognosis of BOT is excellent (99% of long-term in stage I disease [5]), this dogma has been abandoned and several teams chose a more conservative surgery in order to favor subsequent fertility of young patients treated for BOTs. In the last 5 years, several articles of interest have dealt with this conservative management and fertility results.

1. Search strategy and selection criteria

Studies for this review were identified by searches of the PubMed databases with the search terms: “borderline”, “ovarian tumour”, “ovarian cancer”, “conservative surgery”, “ovarian stimulation”, “fertility”, “ovarian induction” and “In vitro fertilization/IVF” with search limitation from 1972 to June, 2005. Papers analyzed in this review were papers published in English (or at least with an abstract in English containing

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the number of patients treated conservatively and their outcomes) including: (1) more than 15 cases of conservative management of borderline tumour with early stage disease (analysis of recurrences) and/or (2) 10 patients treated conservatively for borderline tumour wishing to be pregnant (analysis of spontaneous fertility results). For the analysis of the outcomes of patients with advanced stage disease (ovarian tumour with peritoneal implants) and infertile patients treated using ovarian induction and/or IVF procedure all papers, even cases reports, were analyzed.

2. Standard treatment of BOTs

The basic treatment for borderline tumours is surgery. In most cases, this is the exclusive treatment. Indications of adjuvant therapy remain rare in this pathology (patients with invasive peritoneal implants or with nodal spread located near the nodal sinus) and no randomized studies have demonstrated the advantage of adjuvant therapy on survival in these rare indications.

The surgical procedure begins with a careful exploration of the ovary and abdomino-pelvic cavity. A systematic peritoneal cytology should be performed before manipulation of the ovarian tumour. When the ovarian tumour appears to be malignant, a frozen section analysis should ideally be performed and could then be carried out on oophorectomy or cystectomy specimens. Nevertheless the accuracy of this exam is lower in BOTs compared with malignant or benign ovarian tumours. The accuracy of this frozen section analysis depends on several factors: the size of the tumour, the histologic subtype and the experience of the pathologist himself. The accuracy of this exam is less in mucinous BOTs compared to other histologic subtypes [6,7].

The surgical treatment of the borderline ovarian tumour itself is "historically" radical and based on bilateral salpingo-oophorectomy. This radical treatment was considered as the standard management to reduce the rate of recurrence in invasive form. The addition of a systematic hysterectomy was considered a standard in invasive carcinoma. The hysterectomy has two aims: (1) to diagnose endometrial carcinoma and; (2) to diagnose microscopic peritoneal implants on the surface of the uterine serosa. But in borderline tumours, no studies have demonstrated the interest of such systematic hysterectomy.

Staging surgery is a crucial point and should be associated with the treatment of the ovarian tumour in order to ensure the exact stage of the disease [4]. But in two recent studies, only 12–29% of patients were adequately staged even in cases where frozen section analysis confirmed the diagnosis of borderline malignancy [8,9]. Furthermore, in 34% no biopsies were carried out [8,9]. The staging procedure should include peritoneal cytology (if not performed when treating the adnexal tumour), infracolic omentectomy or large omental biopsies and random peritoneal biopsies. The staging surgery upstage 13–22% of patients with apparent stage I disease, because microscopic implants were discovered on surgical specimens [10,11]. Appendectomy should be classically added particularly in mucinous tumour. Pelvic and para-aortic node areas should be explored with at least palpation. Lymphadenectomy or selective adenectomy should be performed in case of adenomegaly. But complete systematic lymphadenectomy should not be systematically performed in early stage disease [12,13]. The staging surgery could be performed at the time of surgical treatment of the ovarian tumour (when the diagnosis of borderline malignancy is confirmed) or during a second-surgical surgery, the so-called restaging surgery (case of borderline malignancy not diagnosed during the first surgery and only found at the time of permanent histologic analysis).

Nevertheless four recent retrospective studies seem to demonstrate that, even if such staging procedures are beneficial (microscopic implants were discovered whereas macroscopic exploration was normal), these procedures have no impact on the patients' survival [12,14–16]. These results could be easily explained as most patients upstaged after staging or restaging surgery, are upstaged on the basis of isolated positive peritoneal cytology and/or the discovery of microscopic noninvasive implants on the omentum or random biopsies [10,11,14–22]. In BOTs these two findings have no impacts on subsequent treatments. The only case where the management of BOTs limited to the ovary (stage I according to the FIGO classification) is modified after the result of staging surgery is when occult invasive implants are discovered at the time of histologic analysis of macroscopically normal peritoneum or omentum. When we summarize all the data collected in the literature about staging or restaging surgery, this situation is exceptional and was reported in only two cases [14,20]. The only histologic subtype where such situation could be observed is in a case of micropapillary serous tumour [23]. In such pattern invasive implants were frequently associated to serous BOTs [23].

It is for these different reasons that clinicans are now discussing the omission of restaging surgery as long as the initial surgery is not complete (because diagnosis of borderline tumour is not stated during surgery). But such considerations can only be discussed if the following criteria are respected: (1) if the BOT is of serous or mucinous subtype and without micropapillary patterns; (2) peritoneum explored and reported as normal on the surgical report of the initial surgery and; (3) the patient agrees with a careful follow-up. If any of these criteria is not fulfilled, restaging surgery should be proposed [15].

3. Conservative surgery

If bilateral salpingo-oophorectomy remains the standard treatment, preservation of spontaneous fertility is not possible after such treatment. In the last five years, several major studies were published about the interest of a more conservative surgery. Such conservative surgery is defined as preservation of the uterus and at least part of one ovary, in order to preserve fertility. Analysis of the literature about conservative management in BOT is difficult, because most of the series are retrospective and the duration of the follow-up is too short (<5 years) to evaluate the exact rate of recurrences. Furthermore, the rate of patients adequately staged varied in series and depended on the center of treatment. Finally, very few retrospective studies had histologic review of the initial slides of the ovarian tumour to ensure the diagnosis of borderline malignancy.

Table 1 – Results of conservative treatment of early stage BOT (only the series including more than 15 cases are presented)

Authors	Number of conservative treatments	Time of follow-up (months)[a]	Number of recurrences	Number of deaths
Julian and Woodruff [24]	15		0	0
Hart and Norris [25]	43	103[c]	1	0
Tazelaar et al. [26]	20	89[b]	3	0
Bostwick et al. [27]	24	85[c]	3	0
Lim Tan et al. [28]	33	78[c]	4	0
Chambers et al. [29]	20	33[c]	2	0
Rice et al. [30]	32	49[b]	0	0
Leake et al. [31]	53	120[c]	5	0
Piura et al. [32]	17	65[b]	0	0
Barnhill et al. [33]	21	42[c]	0	0
Ji et al. [34]	19	87[b]	4	2
Kennedy and Hart [35]	18	99[b]	2	0
Tamakoshi et al. [36]	58	61[b]	0	0
Darai et al. [37]	18	41[b]	4	0
Papadimitriou et al. [38]	18	93[b]	7	0
Chao et al. [39]	25	48[b]	0	0
Chow et al. [40]	23		0	0
Gotlieb et al. [41]	35	57[b]	4	0
Morris et al. [42]	43	68[c]	11	1
Camatte et al. [43]	50	71[c]	7	0
Zanetta et al. [44]	164	70[c]	20	1
Seracchioli et al. [45]	19	42[b]	1	0
Donnez et al. [46]	16	43[b]	3	0
Prat and De Nictolis [47]	21	86[b]	2	0
Chan et al. [48]	25	80[c]	0	0
Maneo et al. [49]	62	61 and 77[d]	18	0
Fauvet et al. [50]	162	60 and 84[d]	27	0
Boran et al. [51]	62	44[b]	4	0

a Time of follow-up for the whole population studied and not specifically conservative surgery.
b Mean time.
c Median time.
d Median time in two groups compared.

These variable numbers could explain the different values of recurrence rates reported in the literature. Data about conservative treatment for BOTs are reported in Table 1 [24–51]. The risk of relapse is increased after this type of surgery compared to radical treatment. This risk is estimated between 0% and 25% (with a median number in most series of nearly 15%) compared to 5% in case of radical treatment [52]. Nevertheless some of these recurrences were observed very late (72 months in the series of Gotlieb; 147 for Morris; and 240 in our own experience) [41–43]. In such cases, it is difficult to distinguish between recurrence from the initial borderline tumour and a new primary tumour. Some general considerations could help to make a distinction between these two hypotheses (laterality or histologic subtypes of both tumours). But when the recurrent disease is of the same histologic subtypes and laterality as the initial tumour, only molecular biological tests (clonality test) will help. Anyhow, this distinction does not make any difference in the management of patients and in different series, late recurrences are considered as a recurrence from the initial tumour.

Two kinds of conservative treatment could be offered: cystectomy or oophorectomy. Based on the literature data, the rate of recurrences is more important after cystectomy (between 12% and 58%) than after oophorectomy [26,28,32,41,52,53]. For Lim-Tan and colleagues [28], this high rate of recurrence could be related to the absence of complete resection of the initial tumour with free margins. This is observed in particular in case of iterative cystectomy (patients with recurrent disease on the same ovary). Lim-Tan et al. [28] recommends performing a complete pathologic analysis of the margins to ensure complete resection. Nevertheless, such pathologic interpretation of section margins in case of cystectomy is very difficult, particularly in case of fragmentation of the tumour during the surgical procedure (especially after laparoscopic cystectomy). Other authors did not get these results as seen in the series of Papadimitriou and coworkers [38]. In that series, even though all 18 patients treated conservatively had complete excision at the time of microscopic examination, seven recurred [38]. So from a practical point of view, analysis of surgical margins after cystectomy does not modify the management of patients and is therefore not performed. This high rate of recurrences after cystectomy is the marker of frequent multifocal lesion in the same ovary, particularly in patients with serous BOTs.

The high rate of relapse implies that the optimal treatment in patients with intraoperative diagnosis of BOT is unilateral oophorectomy, which reduces the risk of relapse. Cystectomy should be performed only in cases of bilateral tumour (with oophorectomy in the contralateral tumour) and/or in patients with only one ovary (previous history of adnexectomy). In

case of relapse on the remaining ovary in the borderline form, another conservative management (cystectomy) may be proposed to these patients, in order to preserve fertility. In our series, eight patients with recurrent BOTs underwent a new conservative surgery of their recurrent disease [43]. We observed six pregnancies in five of these patients [43,53]. In the series from Gotlieb et al. [41], three cases of conservative management of recurrent BOTs are reported. Those three patients were alive after 6 months, 2 years and 7 years of follow-up, respectively [41].

As a large number of BOTs in young patients are misdiagnosed during the initial surgery (absence of frozen section analysis or false negative results from this exam), most borderline tumours are diagnosed after permanent analysis of a cystectomy specimen. Should a new surgical procedure be performed in order to complete the removal of the ovary on the side of the initial tumour? This type of management is discussed in the literature and no series specifically applies to this strategy. Such management could be discussed in patients in whom a restaging surgery should be performed.

No series has focused on the results from contralateral tube at the time of oophorectomy (salpingo-oophorectomy) compared to oophorectomy alone in patients with unilateral tumour. Basically, in patients with bulky unilateral tumour and with a large development in the mesovarium, salpingo-oophorectomy should be preferred (if the contralateral tube is present and macroscopically normal).

In patients with a unilateral ovarian tumour, in order to reduce the rate of relapse on the remaining ovary, some authors performed routine ovarian biopsies in the ovary contralateral to the ovarian tumour. But in several series, no microscopic lesions were found in a macroscopically normal ovary [26,27,53]. Furthermore, these authors observed some relapses on the macroscopically normal ovary that has been routinely biopsied during initial surgery [26,27]. Atleast, this surgical procedure may induce infertility because of post-operative ovarian adhesions. In most teams, therefore, if the initial ultrasonography is normal and does not reveal the presence of suspicious lesions in the depth of the ovary on the opposite side of the ovarian tumour, macroscopic inspection is sufficient. Biopsies should be performed only in case of macroscopic suspicious lesions.

4. Impact of conservative surgery on the survival rate

Does this increased risk of relapse observed after conservative surgery have an impact on the patients' survival? In different large series, the survival of patients is not affected by the use of conservative surgery [26,28,42,44,50]. In the series from Zanetta et al. [44], the disease-free survival of patients treated conservatively for stage I disease was 99.3%. As we can see in Table 1 which summarizes published data about conservative management; only four deaths were related to the use of conservative surgery (Table 1). The first two deaths were reported by Ji et al. [34]. These first two patients had stage IC mucinous tumours. The first one was a 24 year-old primipara treated at 16 weeks of gestation for mucinous unilateral BOT. She underwent adnexectomy. After delivery a contralateral recurrence was treated by simple cystectomy. She recurred under invasive form 8 years later and died of disease 10.8 years after the initial treatment [34]. The second patient was treated using a simple salpingo-oophorectomy for a unilateral mucinous BOT. Fourteen months later she recurred in the form of peritoneal carcinosis and died of disease 4.2 years later [34]. The third death was reported by Morris et al. [42] in 2000. This patient was treated for a serous bilateral tumour with unilateral cystectomy plus contralateral salpingo-oophorectomy without complete staging procedure. She recurred on ipsilateral ovary and died of this recurrence. But the delay between the initial tumour and recurrence was very long (147 months), so we may assume that the invasive recurrence was due to a new primary tumour than recurrent disease [42]. The fourth lethal recurrence was reported by Zanetta et al. [44]. This 30 year-old patient was treated by cystectomy for a stage IC mucinous disease. She recurred 10 months later in the pelvis and abdominal cavity and died of disease 5 months after the diagnosis of recurrence [44]. We observed that in these four exceptional deaths, three patients had mucinous BOTs (two of which were treated using cystectomy).

The fact that the recurrent disease has no impact on survival could be explained by the fact that in several of these studies, no invasive relapse was observed and all recurrent diseases had a borderline histology with excellent prognosis [26,28,43,50]. Furthermore, recurrent diseases were diagnosed using follow-up procedures (based on clinical examination, systematic ultrasonography and/or blood markers-CA 125 or 19.9) [38,43,44].

Reported cases of recurrence in the form of invasive carcinoma for patients with initial stage I disease are exceptional. Such cases are summarized in Table 2 [29,41,44,54]. Zanetta and colleagues [44] recently reported a series of 164 patients who underwent a fertility-sparing surgery for stage I disease. Five cases of progression into invasive ovarian carcinoma were observed, one of them very shortly (9 months) after the initial treatment of the borderline tumour [44]. Four of them were alive after treatment of their recurrences [44]. Gotlieb et al. [41] also reported a case of contralateral ovarian carcinoma, observed 5 months after conservative treatment of a BOT. The characteristics of this invasive tumour (endometrioid carcinoma) were different from those of the initial borderline tumour (mucinous) [41]. This patient was alive with no evidence of disease 33 months after the treatment of the ovarian tumour [41]. Chambers et al. [29] reported a case of a patient with stage IA serous tumour treated by initial cystectomy who recurred 1 year later in the form of stage IIA serous carcinoma. The outcome of this patient has not been reported. Lastly in our institution, we observed the case of a patient who recurred in the form of invasive carcinoma on the ipsilateral ovary 2 years after a cystectomy for a unilateral mucinus tumour. Adjuvant therapy is currently being delivered to this patient [54]. Altogether only eight cases of invasive recurrences in patients with stage I borderline tumour has been reported in the literature, whereas more than 1000 of such treatment cases have been published (Table 1). So, the risk of recurrence in the form of invasive carcinoma is exceptional and could be estimated at <1%.

These data seem to confirm that, even though the risk of relapse is increased after a conservative treatment of BOT, this conservative management does not alter survival of

Table 2 – Reported cases of recurrence in the form of invasive ovarian cancer in patients with stage I disease

Authors	Stage	Histologic subtype	Age (years)	Initial treatment of the ovarian tumor	Site of recurrence	Time (months)
Zanetta et al. [44]	IC	Mucinous	30	Cystectomy	Pelvis + Peritoneum	10
	IA	Serous	41	Cystectomy	2 Ovaries + nodes + peritoneum	39
	IC bilat	Serous	40	Cystectomy + adnexectomy + chemotherapy	Contralateral ovary	40
	IA	Mucinous	27	Cystectomy	Ipsilateral ovary	55
	IA	Serous	36	Adnexectomy + staging	Contralateral ovary	39
Chambers et al. [29]	IA	Serous	?	Cystectomy	Ipsilateral ovary	12
Gotlieb et al. [41]	IA	Mucinous	35	Adnexectomy + staging	Contralateral ovary	5
Salomon et al. [54]	IA	Mucinous	23	Cystectomy	Ipsilateral ovary	26

patients. So, conservative surgery could be safely performed in young patients treated for BOT and should be provided with careful follow-up.

5. Limits of conservative surgery

Are all young patients with BOT eligible for conservative treatment? Such procedures could be safely offered to patients with an early stage disease. Nevertheless several questions remain unanswered on the limits and indications of such treatment. First are the technical limits of a conservative surgery ("feasibility limit") in patient with initial bulky bilateral tumour with massive involvement of both ovaries (or the last ovary in patients with previous history of unilateral oophorectomy). In such cases, preservation of at least a part of one ovary is not feasible because no part of an apparent healthy ovary could be preserved. In such patients, bilateral oophorectomy should be performed but with the preservation of the uterus.

The second limit concerns the indications of such conservative surgery. Should such management be performed at any stage of the disease? Data on conservative management in serous BOT with peritoneal implants are rare in the literature and are summarized in Table 3 [36,42,44,46–49,51,55,58]. To date, only two major series have been published [44,57]. These two series conclude that conservative management may be proposed to patients with peritoneal implants, provided that these implants are entirely removed, with reliable pathologic interpretation [44,57]. Zanetta and colleagues have reported 12 patients with noninvasive implants treated conservatively: three of them had BOT recurrence in the spared ovary and one had progression into invasive ovarian carcinoma, but was saved by surgery and chemotherapy. All these patients are presently disease free [44]. In our institution, we have reported a series of 17 patients with a complete obstetrical follow-up, and who were treated conservatively for a BOT with peritoneal implants. The rate of ovarian recurrences in the form of borderline tumours on the spared ovary is high in this subgroup of patients (7/17). We observed that two patients had an invasive evolution of borderline peritoneal implants (one of them with invasive implants during initial treatment). But none of these patients had an ovarian carcinoma in the spared ovary [57]. So the rate of peritoneal recurrence does not seem to be affected by the use of conservative surgery [44,57]. The survival rate of patients with BOT and peritoneal implants treated conservatively is not different from that of patients treated radically [44,59]. Such data suggest that conservative surgery should be considered for patients with noninvasive implants.

But is it possible to propose such management to patients with invasive peritoneal implants, which are considered as more aggressive? Zanetta et al. [44] reported the case of seven patients with invasive implants treated conservatively. Five recurrences were observed (borderline tumour in the spared ovary), but all patients were saved by surgery [44]. In our experience, we have performed this treatment in three patients with invasive implants, one of them with evolutive peritoneal disease [57]. Table 3 summarizes all the reported cases of conservative management for advanced stage BOTs and shows that only three deaths have occurred [36,47]. The first case was reported in the recent paper of Prat and De Nictolis [47]. This patient was initially treated with unilateral salpingo-oophorectomy followed by adjuvant chemotherapy for BOT with invasive implants. She died of disease 9.3 years after the treatment of her ovarian tumour but we have no details about the site of the recurrence [47]. Considering such observations with aggressiveness and bad prognosis of BOTs with invasive peritoneal implants, the use of conservative surgery in such patients is more debatable [57]. The other two patients who had lethal evolution after conservative management for advanced stage disease had similar clinical evidence: stage IIIB or IIIC BOT with mucinous subtype and incomplete surgical resection (residual disease <2 cm in one case and between 2 and 5 cm is the other) [36]. Both patients died 9 and 72 months following the treatment, respectively [36]. This evolution is probably more related to the natural history of such aggressive disease (peritoneal pseudomyxoma) which was incompletely resected than to the use of conservative surgery [36]. Nevertheless conservative treatment is not a good indication in patients with mucinous BOTs and peritoneal spread.

Other questions on the limits of conservative surgery for BOTs remain unsolved to date: is conservative surgery safe for patients with early stage mucinous subtype? Could conservative surgery be safely proposed to patients with micropapillary patterns? We need further clinical research and data to study these points.

Table 3 – Results of conservative management of advanced stage borderline tumors

Series	Number of patients	Type of implants	Number of recurrences	Number of deaths	Number of pregnancies
Zanetta et al. [44]	25	7 Invasive/18 noninvasive	5 (Contralat. ovary)	0	?
Beiner et al. [55]	4	NP	3 (Borderline/contralat. ovaire)	0	?
Morris et al. [42]	3	NP	2 (1 Borderline/contralat.ovaire + 1 peritoneum)	0	1
Tamakoshi et al. [36]	4	NP	3	2	?
Miller et al. [56]	1	Noninvasive	0	0	1
Donnez et al. [46]	2	Noninvasive	0	0	?
Camatte et al. [57]	17	3 Invasive/14 noninvasive	9 (7 Borderline/controlat. ovaire + 2 peritoneum)	0	7 in 6 patients (3 after conservative treatment of recurrence)
Prat and De Nictolis [47]	10	1 Invasive/9 noninvasive	3 (2 Borderline/contralat. ovary)	1 (Invasive implants)	?
Chan et al. [48]	1	NP	0	0	1
Maneo et al. [49]	1	NP	NP	0	?
Lackman et al. [58]	2	Noninvasive	1	0	1
Boran et al. [51]	1	Noninvasive	0	0	0

6. Spontaneous fertility results after conservative surgery

The first aim of conservative surgery is to preserve subsequent fertility in young patients. But it is difficult to analyze fertility results reported in the literature because in the few series involving addressing this crucial point, informations are incomplete. Fertility results are detailed in Table 4 [41–44,46,50,51]. Seven series specifically reported the fertility results of conservative treatment [41–44,46,50,51]. In the series involving the largest number of patients treated conservatively, fertility results are not detailed [44]. We only know that 44 pregnancies (with normal outcomes in 41) were observed in 44 patients [44]. Thus, Gotlieb et al. [41] reported 22 pregnancies (in 15 patients) on a series of 39 patients treated conservatively. But the number of patients who wished pregnancy is not indicated. In the series of Donnez et al. [46], 11 patients wished pregnancy and seven of them obtained 12 pregnancies. In the series of Morris, 24 out of 41 patients treated conservatively wished to obtain a pregnancy. Twelve patients obtained 25 pregnancies (with 16 normal outcomes) [42]. In our own series on 42 patients treated conservatively, 13 patients did not wish a pregnancy. Twenty-six pregnancies (24 obtained spontaneously) were obtained in 19 patients. Among patients with stage II/III disease, seven pregnancies were observed [43]. In a recent paper from Boran et al. [51], 25 of 62 patients treated conservatively wished to obtain pregnancy and 10 succeeded (with 13 pregnancies observed).

One of the most important series specifically dealing with this question was recently published. It concerned 65 patients (among 162 treated conservatively) who wished to obtain pregnancy [50]. Thirty pregnancies (27 spontaneous) were obtained. The characteristics of patients who obtained pregnancy (parity, previous history of infertility, histologic subtype, stage, type of conservative surgery, surgical approach) were not different from patients who did not obtain pregnancy [50]. The only difference was the patients' ages who were significantly older in the group of patients who did not obtain pregnancy (32 versus 26 years old) [50]. The conception rate was 42% in patients aged under 35 compared to 22% in patients aged between 35 and 40. No pregnancies were observed in patients aged >40 and treated conservatively [50].

The choice of the surgical approach could theoretically affect the fertility results. Some series recently reported their results about the use of laparoscopic approach in the management of BOT [45,60–62]. These different series suggest that laparoscopic surgery could be safely proposed in selected cases of patients with BOTs without increasing the risk of recurrence [61]. The advantage of such an option is that it reduces the risk of post-operative adhesions which can reduce the success of subsequent fertility in young patients. So in the series reported by Seracchioli et al. [45] on 19 young patients treated using a strictly laparoscopic approach for stage I BOTs, 10 patients wanted pregnancy and six conceived. But in the large series published by Fauvet et al. [50], there was no impact of the surgical approach on fertility rate.

So, the spontaneous fertility rate reported in the literature varies between 32% and 65% [43,50]. Globally, we can estimate that half of the patients treated conservatively will obtain spontaneous pregnancy. But such results are low in patients

Table 4 – Fertility results after conservative treatment (only the series involving more than 10 patients desiring pregnancy with clinical outcomes of pregnancies obtained are included)

Series	Number of conservative treatments	Patients wishing of pregnancy	Number of pregnant patients	Number of pregnancies	Outcomes pregnancy
Gotlieb et al. [41]	39	?	15	22	19 Normal (with 3 caesarean) 3 Ongoing
Morris et al. [42]	43	24	12	25	16 Normal 4 Miscarriages 3 Ectopic pregnancy 2 Ongoing
Zanetta et al. [44]	189	?	44	44	41 Normal 3 Miscarriages
Camatte et al. [43]	68	29	19	26	16 At term 3 Miscarriages 1 Ectopic pregnancy 4 Abortions 2 Ongoing
Donnez et al. [46]	16	11	7	12	All normal
Fauvet et al. [50]	162	65	21	30	17 At term (with 2 caesarean) 5 Miscarriages 8 Abortions
Boran et al. [51]	62	25	10	13	3 Abortions 10 Normal

aged >40 and conservative surgery to preserve subsequent fertility should not be proposed to this patient group.

7. Management of infertility in patients treated for BOTs

Infertility is frequently observed in patients with BOTs. In the various series published, 10–35% of patients had previous history of infertility before the treatment of their ovarian tumour [41–43,50]. So, in spite of conservative management for BOT, some of these patients will experience infertility. Can we propose ovarian stimulation or in vitro fertilization (IVF) to these patients, when a number of studies incriminate hyperstimulation in the genesis of ovarian cancer? Such options should be discussed with the patient as the association of ovarian stimulation and risk of ovarian cancer remains unclear. Nevertheless two recent experimental studies on in vitro cell culture suggest that estradiol or follicle stimulating hormone (FSH) had no deleterious impact on cell proliferation [63,64]. On the contrary, one of the studies showed that human chorionic gonadotropin (HCG) reduces the proliferation of cell line [64]. These important results seem to suggest that ovarian induction could be used in patients treated for BOTs.

As regards this specific case, clinical data reported in the literature exist but are rare. All these cases are summarized in Table 5 [43,50,55,65–70]. In the recent study by Fauvet et al. [50], 11 patients underwent ovarian stimulation (5 cases), intra-uterine insemination/IUI (1 cases) or IVF procedures (5 cases). Three pregnancies were obtained (2 after IVF and 1 after IUI). The clinical outcomes of these patients are not detailed but we know that in this series none of the patients died [50]. The largest multicentric experience on 16

Table 5 – Literature review of patients with previous history of BOT who underwent ovarian stimulation or in vitro fertilitization (IVF) procedures for infertility treatment

Series	Number of patients	Number of ovar. inductions	Number of IVFs	Number of stages II/III	Number of pregnancies	Number of recurrences (after stimulation)
Nijman et al. [65]	1	0	1	1	1	0
Mantzavinos et al. [66]	2	0	2	2	1	0
Hoffman et al. [67]	1	0	1	1	1	0
Madelenat et al. [68]	16	0	16	2	5	0
Beiner et al. [55]	7	0	7	2	5	2
Camatte et al. [43]	5	1	4	2	2	2 (Borderline/preserved ovary)
Attar et al. [69]	1	0	1	1 (III C)	1	Rapid evolutive peritoneal disease
Fasouliotis et al. [70]	5	0	5	0	6 Pregnancies in 3 patients	3 Recurrences of borderline form in the same patient
Fauvet et al. [50]	11	6 (with 1 intrauterine insemination)	5	1	3	?

patients previously treated conservatively for BOT and who underwent IVF procedures was reported by Madelenat et al. [68]. With a mean follow-up of 46 ± 36 months, no relapse was reported for these patients. Five pregnancies were obtained [68].

Thus, it seems possible to propose hyperstimulation to patients with stage I BOT without affecting the patients' prognosis. But as the literature is still poor on this subject, we think that the number of stimulation cycles should be limited, in order not to increase the potential risk of recurrence. Literature data concerning the safety of hyperstimulation in patients with peritoneal implants concern series involving only a small number of patients (Table 5). Nijman, Mantzavinos and Hoffman [65–67] mentioned a total of five patients treated successfully with IVF procedure for stage II or III serous BOTs with noninvasive implants. But recently Attar et al. [69] has reported a rapid progression of peritoneal disease in a patient with stage IIIC serous tumour with a micropapillary pattern. Thus, it does not seem possible to give guidelines concerning hyperstimulation and IVF in patients with advanced stage disease and/or micropapillary patterns.

When conservative management is not technically feasible because of the presence of a massive spread of ovary, bilateral salpingo-oophorectomy should be performed in patients with bilateral massive BOT and/or a BOT relapse on the remaining ovary. But in such cases, the uterus should be preserved. Pregnancies have been reported in this context with an ovocyte donor or successful transfer of frozen embryos, obtained before bilateral salpingo-oophorectomy [71–73]. The case reported by Gallot et al. [71] is of particular interest. This patient presented an ovarian recurrence 6 months after a conservative treatment of stage IIIA serous BOT [71]. An IVF procedure was performed in emergency before the surgical procedure (with the recovery of frozen embryos). Completion surgery was then carried out (with preservation of the uterus) and the patient obtained subsequent pregnancy after transfer of embryos [71]. Such clinical management should be discussed in selected cases.

It is also possible to propose a cryo-conservation of ovarian tissue (if the selection of a healthy part of the ovary is feasible) at the time of the surgical procedure to patients for whom a bilateral salpingo-oophorectomy (or unilateral in patient with a single adnexa) has to be considered. A case of pregnancy was recently observed for the first time in a human being after such a procedure [74]. Two other pregnancies are still ongoing. But the indication of this procedure remains unclear in patients with BOTs.

8. Follow-up after conservative treatment

Very few papers deal with follow-up after conservative management for BOT [38,75]. The paper of Zanetta et al. [75] is the most complete and interesting on this question. It involves 164 patients treated conservatively for stage I disease. All patients were followed up every 3 months for 2 years (with clinical examination + abdominal and vaginal ultrasonography (US)). Patients were followed up every 6 months thereafter. CA 125 levels were carried out every 6 months in patients with serous tumours. Twenty-eight patients recurred but 24 had complete details of follow-up procedures available [75]. All patients had abnormal US (23 patients had ovarian mass diagnosed on routine US and one had persistent free fluid). Seven had palpable mass that were discovered during clinical examination and seven had abnormal CA125 level. The most useful procedure was the abdominal and vaginal US [75]. The interest in blood markers in the follow-up of patients treated conservatively remains an issue that is discussed. In the other paper, modalities of follow-up were similar to the study of Zanetta [44]. The authors specified that all patients had raised CA 125 level and the presence of ovarian cyst on US [38]. However, the precise number of patients with exclusive elevation of CA 125 remains unknown. The authors state that all recurrent patients had CA 125 levels slightly or moderately high [38]. Nevertheless the authors suggest combining routine US & markers (CA 125 in serous tumour and 19.9 in mucinous tumour) to follow-up patients.

Such follow-up should be continued after 5 years because, as we have seen, very late recurrence could be observed (after 20 years). In the series of Papadimitriou, all recurrences were observed after 6 years following the treatment of the ovarian tumour [38]. In the report of Tropeet al. [4], 20% of recurrences were observed at least 5 years after the surgical treatment of BOT. Such follow-up should also be continued after obtaining pregnancies, because in several series some recurrences were observed in patients who obtained pregnancies (all patients who recurred in the series of Papadimitriou) [38].

If pregnancies are obtained, should the ovary be removed? Such routine procedure remains controversial [50,53] and discussion of this option depends on several factors (histologic subtype, stage, type of conservative surgery; and the patient's own wish). Even if we consider that the rate of recurrences is between 0% and 35% (<15% in patients treated with oophorectomy), it means that routine oophorectomy is useless in 65–100% of cases (in more than 85% of patients treated with oophorectomy). Furthermore, these recurrent diseases (borderline type in most cases) could be easily cured, using a simple surgical procedure. So, several teams suggest that systematic removal of the spared ovary is not mandatory provided that patients have regular follow-up. Oophorectomy is then only proposed in cases of relapse. However, some patients prefer to undergo oophorectomy after pregnancy, for psychological reasons or because the patient wished to simplify the modality of follow-up procedures.

Previous history of BOT is not a contra-indication for the use of substitutive hormone replacement therapy.

9. Conclusions

BOTs compared to ovarian carcinoma are characterized by: (1) occurrence 10 years earlier than ovarian cancer and; (2) an excellent prognosis with a 10-year survival close to 100% in patients with stage I disease. One third of BOTs are diagnosed in patients aged under 40 for whom a treatment preserving fertility-potential could be discussed. Such conservative surgery, defined by the preservation of the uterus and at least part of one ovary, could be safely performed in patients with at least stage I disease. Such treatments increase the rate of recurrences (between 15% and 35% depending on the type

of conservative surgery), but without any impact on the survival of patients because most of the recurrent diseases are in the borderline form, that are easily cured and with excellent prognosis. The spontaneous pregnancy rate is nearly 50%. In case of persistent infertility, it seems that the use of ovarian induction or IVF procedures could be proposed in selected cases. Follow-up is essential and should be based on clinical examination and routine ultrasonography, while the benefits of CA 125 level determination remains under discussion. Follow-up should be prolonged after 10 years because cases of late recurrence are reported in the literature. The interest in completion surgery (removal of the retained ovary) in patients after obtaining pregnancy remains debated.

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