REVIEW ARTICLE

Oncologic and reproductive outcome after fertility-saving surgery in ovarian cancer

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Summary

The rate of ovarian tumour diagnosis in reproductive age woman has increased parallel to the improvements in diagnostic methods and regular gynaecological visits. Because of this organ saving surgical procedures for the preservation of reproductive and endocrine functions have gained more interest. Conservative surgical approaches for ovarian tumours after surgical staging include cystectomy, unilateral salpingo-oophorectomy and unilateral salpingo-oophorectomy plus contralateral cystectomy. Ovarian tumours diagnosed in young ages tend to be low-stage low-grade malignancies. This not only enables but also necessitates preserving the fertility of women who have not completed their family.

In invasive ovarian cancer, fertility saving surgery is confined to early-stage and low-grade disease. But, it also had been reported in advanced stages (up to Stage IIIc). Candidates for those procedures were selected according to the FIGO stage, grade, ploidy state, histological subtypes and patients' desire. Adjuvant chemotherapy is necessary for high-risk patients. The rate of recurrence following conservative and radical surgical procedures in low-stage and low-grade tumours are 9% and 11.6%, respectively; and disease-free and overall survival rates do not differ significantly.

Prognosis of borderline ovarian tumours is excellent. Five and 20-year survival rates are 95% and 80%, respectively. Management of borderline tumours has evolved significantly in the last few decades. In contrast to invasive ovarian cancer, borderline tumours can be operated on conservatively at all stages. Chemotherapy is rarely prescribed even in advanced stages.

Eighty percent of malignant germ cell tumours are diagnosed less than 30 years of age, and 70-75% of patients have Stage I disease. Conservative surgery is generally used in malignant germ cell tumours even in advanced stages.

The relation between ovulation induction and tumour recurrence is not consistent in the literature. Spontaneous pregnancy rates following fertility saving surgery has been reported as 60-88%. Because of this over-treatment of these patients for fertility should be avoided.

Briefly, fertility saving surgery can be performed safely in germ cell, borderline and early stage epithelial ovarian tumours in selected cases. Any increment in the rate of tumour recurrence following ovulation induction has not yet been demonstrated. Menstrual irregularities caused by chemotherapy are transient. The congenital malformation rate of ovarian cancer patients is slightly higher than that of the normal population, but no significant difference has been observed between patients who received or did not receive chemotherapy.

Key words: Ovarian cancer; Fertility saving surgery; Oncologic outcome; Fertility outcome.

Introduction

Ovarian cancer is the second most common malignancy among all gynaecologic malignancies. The rate of ovarian tumour diagnosis in women of reproductive age has increased in the last decades. The possible explanation for this increment may be the improvements in primary healthcare and diagnostic methods. FIGO reported that 8.7% of the invasive epithelial tumours and 31.8% of the borderline epithelial tumours were diagnosed in patients younger than 40 [1]. Eighty percent of malignant germ cell ovarian tumours are diagnosed less than 30 years of age.

In these patients, preservation of reproductive and endocrine functions are crucial. Therefore, fertility saving surgical procedures have gained importance in recent years. Authors are in agreement on the convenience of conservative surgery for the treatment of borderline, germ cell and early stage-grade invasive ovarian carcinomas, but some points in the management of these patients still remains to be enlightened [2-6]. Basically, there are four important questions to be addressed: 1 - Does fertility saving surgery affect oncologic and reproductive outcome? 2 - Does ovulation induction affect oncologic and reproductive outcomes following the fertility saving surgery? 3 - Does adjuvant chemotherapy affect reproductive and endocrine physiology? 4 - Does the rate of fetal anomalies increase by these treatment modalities? In this review, all these questions will be discussed.

Conservative surgery in epithelial ovarian carcinoma

Three to seven percent of epithelial ovarian carcinomas are diagnosed before 40 years of age, and 7-8% of Stage-1 epithelial ovarian carcinomas are seen in patients before age 35 [7, 8]. Tumours diagnosed in young patients are more likely to be in lower grades and stages. For these patients, preservation of reproductive potential is essential. Five-year survival rates in early stage invasive epithelial ovarian carcinomas have been reported to be 62-85%. This rate is 95% for Stage 1A [9-11]. These high rates of five-year survival led to the initiation of fertility saving surgical procedures in the management of early-stage invasive ovarian carcinoma in young patients. Todays, authors are in agreement on the management of early-stage invasive epithelial tumours of the ovary by fertility saving surgery (FSS). In this manner, instead of the conventional approach (hysterectomy and bilateral salpingo-oophorectomy) in the management of early stage-low grade tumours (Stage 1A-IB, Grade 1-2), conservative approaches can be used [7] (Figure I). Although the reports of FSS up to Stage IIIc are present in the literature, this approach is not recommended for patients who have completed their childbearing and/or are in advanced stages [12-15].

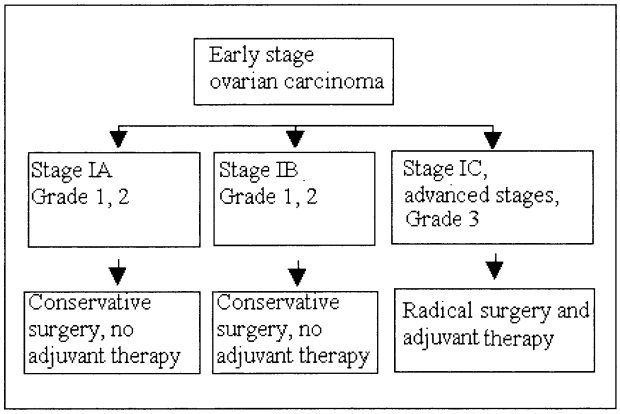

Figure 1. — Fertility saving surgery in early-stage epithelial ovarian cancer.

Conservative surgical procedures are cystectomy, unilateral salpingo-oophorectomy and unilateral salpingo-oophorectomy plus contralateral cystectomy [2-6]. Even if both of the ovaries are ectomised, preservation of the uterus for ovarian-cryopreservation or oocyte donation is a chance for future fertility [7].

The first step in the management of ovarian tumours is surgical staging. By proper staging, prognosis of cases in which the disease is really confined to the ovaries is excellent. However, five-year survival rate decreases significantly in Stage 1A cases who were not properly staged [16]. A higher stage of the disease is likely to exist in approximately 30% of improperly staged ovarian tumour cases [17, 7].

In surgical staging, following an appropriate incision, samples should be collected for cytological examination, the whole abdominal cavity should be evaluated, infracolic omentectomy, appendectomy (especially for mucinous tumours), and pelvic-paraaortic lymphadenectomy should be performed. Regarding the 5% co-existence of ovarian tumours and endometrial carcinoma, endometrial sampling is necessary for all cases [18]. Evaluation of the contralateral ovary and lymphadenectomy may be omitted in low-risk patients but must be performed in high-risk patients [18]. In our clinic, we perform pelvic and paraaortic lymphadenectomy in all cases of invasive ovarian carcinoma. Today, if the contralateral ovary is macroscopically normal (by inspection and palpation), wedge biopsy is not indicated in the conservative approach. The reasons are first, the very low risk of involvement in such cases [4, 19]; second, infertility due to adhesion formation [20], and third, the risk of possible ovarian failure following multiple ovarian biopsies [4]. But, specifically in serous tumours 30% of contralateral involvement should be considered [7].

There are two critical points in FSS: 1 - the preservation of fertility potential; 2 - effects of the procedure on disease-free and overall survival rates. Thus, high- and low-risk groups should be determined before choosing this approach. In epithelial ovarian tumours, prognostic factors include FIGO stage, grade, ploidy state, histological subtypes, and Ca-125 levels [18].

Oncologic outcome

One of the largest series in the literature was reported by Zanetta *et al.* Fertile and oncologic outcomes of 56 conservatively and 43 radically operated patients were compared. Recurrence rates of FSS and radical surgery groups were 9.0 and 11.6%, respectively without any significant difference. Disease-free and overall survival rates were also similar. However in conservatively operated patients, the recurrence rate of well differentiated tumours was 3.6%, while those of moderately and poorly differentiated tumours were 17% and 21%, respectively [2].

In the study of Colombo *et al.* [12], results of 56 conservatively operated and 43 radically operated patients were compared. In Stage IA with a 75-month follow-up period, the recurrence rate was 8.4% in the conservatively treated group, and 8.7% in the radical surgery group. There were no relapses among conservatively managed Stage IB and IC patients, however there was a 15% relapse rate in the radically managed group. The authors concluded that conservative surgery can be performed in FIGO Stage I disease regardless of the histologic type and the grade of tumours.

Data of the conservatively managed 25 ovarian cancer patients with a 47-month median follow-up period were reported by Morice *et al.* [3]. The recurrence rate was 28%. The 5-year disease-free and overall survival rates were 64% and 82%, respectively. These rates were 80% and 90%, respectively in Stage IA. The disease-free survival rate at five years for patients with Stage IA grade 1 and 2 tumors were 89% and 71%, respectively. The authors concluded that Stage IA, grade-1 patients who were willing to preserve their fertility potential were appropriate candidates for conservative surgical procedures, but that patients with more advanced diseases than Stage IA were not. In contrast, Raspaglisein's study [13] showed no recurrence in ten high-risk invasive epithelial ovarian carcinoma patients. Moreover, Miyazaki *et al.* [14] reported a 14% recurrence rate for cases earlier than Stage IIC following FSS.

Reproductive outcome

In some of the studies mentioned above, many pregnancies were obtained following conservative procedures. In Colombo's series, 25 conceptions were achieved in 17 patients (16 healthy newborns, one twin, two ectopic pregnancies, four abortions, and four elective terminations). In a study of Morice *et al.* [3], in 18 patients without recurrence, menses had completely ceased in only one patient who had been treated with adjuvant radiotherapy. The remaining 17 patients had menstrual abnormalities and pregnancies were achieved in only four of them. All four pregnant patients were followed-up to an average of 70 (24-238) months and no relapse was observed. In a study of Zanetta *et al.*, among 55 conservatively operated patients, 16 had adjuvant chemotherapy (29%). All the patients treated with chemotherapy had normal menstrual function during or after the treatment, and no ovarian failure was observed. Seventeen normal pregnancies were achieved, and all of them delivered either by vaginal or abdominal routes. Two ectopic pregnancies, four spontaneous abortions and four elective terminations were also reported [2]. In the study of Raspaglisei *et al.* [13], except one, all of the patients who received chemotherapy had normal menses. Five of them conceived and three patients gave birth successfully. Likewise, normal menstrual cycles returned and 18 pregnancies were achieved in the study of Miyakazi *et al.* on 16 patients [14].

Zanetta speculated that, even for Stage IB tumours, FSS can be considered if the tumour is well differentiated and an adequate portion of the normal ovary is preserved [2]. On the other hand, FSS is not recommended in Stage IA-grade 3 and more advanced stages, clear cell tumours, and high-risk cases according to the DNA flow cytometric analysis [3]. For low-risk patients, FSS is the adequate mode of treatment. Postoperative chemo- or radiotherapy is not necessary.

The decision to use adjuvant chemotherapy for women with early-stage epithelial ovarian cancer should be based on stage and histologic grade of the tumour. Patients with Stage IA or IB ovarian cancer do not require adjuvant chemotherapy as they have an excellent prognosis (more than 90% survival at five years) [21]. Adjuvant chemotherapy may be beneficial in high-risk early-stage ovarian cancer (Stage IC and Stage II). Cisplatin-based regimens appear to be superior to melphalan and other regimens for patients with Stage II disease [22]. In the report of Zanetta *et al.*, adjuvant chemotherapy was given following FSS to Stage IB-grade 1 and more advanced stages [2]. In our clinic adjuvant chemotherapy was given to Stage IB-grade-3 and more advanced stages of ovarian carcinomas. Ovarian functions were either preserved or came back following adjuvant chemotherapy [2, 7, 23].

Conservative surgery in borderline ovarian tumors

The term 'borderline' or 'low malignancy potential' was first been defined by Taylor in 1929; it was characterised by histologically significant epithelial proliferation without stromal invasion [24]. Prognosis of borderline tumours is excellent. Five- and 20-year survival rates are 95 and 80%, respectively [25, 26]. In young patients, borderline tumours are more frequent than invasive forms [4]. Borderline tumours constitute 10-15% of ovarian carcinomas at all ages, and 75% of those diagnosed before 40 [27, 28].

Management of borderline tumours has evolved significantly in the last few decades. Radical surgery has been mostly abandoned because of the low yield of upstaging, and rare usage of chemotherapy in advanced stages [7] (Figure 2). Tumour stage is still the most important prognostic factor today. Death rates have been reported to be 1.9% in Stage 1, and 21% thereafter [29] which is why we advise full staging surgery but no adjuvant therapy. In Stage I borderline tumours, surgery is sufficient. Cure rates of early stage mucinous and serous tumours have been reported to be 90% and 100%, respectively [30, 31].

A long period of survival, late recurrence and low stage-grade are the factors that should orient us to conservative approaches for women in childbearing ages [32-35]. Oncologic and reproductive outcomes of borderline epithelial ovarian tumours following conservative surgery will be discussed below.

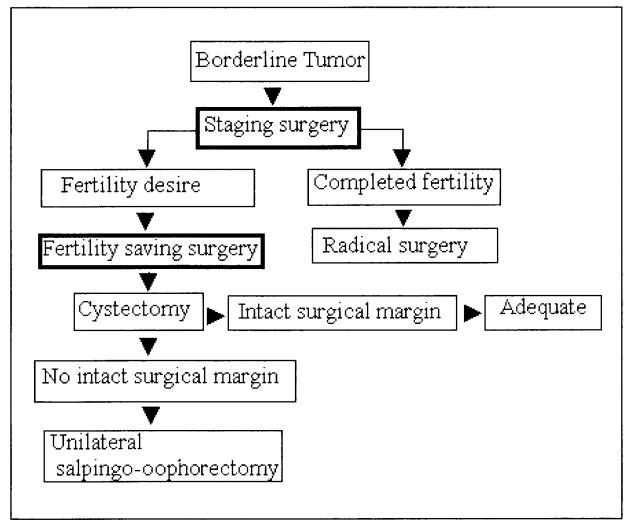

Figure 2. — Management of borderline tumors.

Oncologic outcome

Recurrence rate of borderline tumours is higher in conservatively treated than in radically operated patients [4, 36]. The highest recurrence rate has been reported in the cystectomy group. In Morice's study [27], tumour recurrence rates in radical surgery, salpingo-oophorectomy and cystectomy groups were found to be 5.7, 15.1 and 36.3%, respectively. Similar data were reported by Tazelaar, Lim-Tan, Darai, and Morris [26, 29, 37, 38]. The issue of ovarian cystectomy in contrast to a complete oophorectomy is to further preserve fertility potential. According to the data from a small number of cases the recurrence rate after a cystectomy is in the range of 12 to 15%, similar to the recurrence rate after salpingo-oophorectomy [39]. In summary, the type of conservative surgery affects recurrence rates which may necessitate further surgical operations but does not change overall survival rate significantly [4].

In contrast to invasive tumours, FSS can be performed in advanced stage borderline tumours [38-40]. The histologic type of the implants affects prognosis dramatically in advanced stage diseases (invasive or non-invasive). Moreover, rates of survival in advanced stage diseases with non-invasive and invasive implants are 95.3 and 66%, respectively [39].

The lack of positive impact of adjuvant chemotherapy on borderline tumours has been demonstrated in numerous studies [41]. The malignant transformation was reported to be 2% by Zanetta *et al.*, which does not coincide with the known rate of 0.75% [36,42]. Furthermore, some authors have reported that de novo progression of invasive carcinomas from peritoneum is more frequent than the transformation from borderline tumours [43]. Consequently, cases managed conservatively must be closely followed-up.

Zanetta *et al.* performed a prospective trial consisting of 339 patients with borderline ovarian cancer [36]. Of these patients, 83.4% had Stage I, 7.9% had Stage II, and 8.5% had Stage III disease. All cases were followed-up for 70 months. A hundred and fifty of them were operated on radically and 189 cases were managed conservatively. Recurrence rates were 4.6% in radically operated patients and 18.5% in conservatively managed cases. Disease-free survival proportions were estimated as 99.6%, 95.8% and 89% in patients with Stage I, II and III disease, respectively. Recurrence rates were reported to be 5.7% in radically operated patients and 51.4% in conservatively managed cases by Morice *et al.* [4]. In the study of Benier *et al.*, 43 cases underwent conservative surgery. Nine of the 43 patients (21%) developed a local recurrence, eight of which occurred in patients with serous tumors [44]. Another report about recurrence rates belongs to Cametta *et al.* In 17 conservatively managed Stage I and II patients, recurrence rate was 17% [45]. Local recurrence rate was noted as 7.6% in the trial of Gotlieb *et al.* [39]. In the report of Seracchioli *et al.* [46], 11 of 19 cases underwent cystectomy and the remaining eight patients were subjected to unilateral salpingo-oophorectomy (all laparoscopically). One patient was Stage IC, two were Stage IB and the remaining 16

were Stage IA. One of the Stage IA patients – a serous type – was the only recurrent case after initial surgery who finally underwent re-laparoscopic cystectomy.

Reproductive outcome

Fertility results are excellent after conservative management of both early and advanced stage borderline tumours in the literature. In one of the recent studies, consisting of 17 patients who were staged as Stage II (6/17) and III (11/17), eight pregnancies were obtained from seven patients. Two pregnancies were achieved by ovulation induction and the remaining six occurred spontaneously. No recurrence was reported in their follow-up period [45]. In Morice's study 17 pregnancies were obtained from 14 patients. Fifteen were spontaneous and 13 of all pregnancies were Stage I, while four were Stage III [4]. In a clinical trial of Papadimitri *et al.*, ten pregnancies were obtained from 15 women and also five from six patients treated conservatively [47]. Ectopic pregnancy rate seems to be rising in the studies which report fertility results after conservative treatment [2, 12, 26]. Adhesion formation because of extensive surgical procedures may be the reason.

Fertility saving surgery in malignant ovarian germ cell tumors

Malignant ovarian germ cell tumours (MOGCT) are less frequent than the epithelial type and consist of less than 5% of all ovarian malignancies [48]. MOGCT can be divided into two main groups: dysgerminomas and non-dysgerminomas. Non-dysgerminomas include endodermal sinus tumours, immature teratomas, mixed germ cell tumours, choriocarcinomas, embryonal carcinomas, and polyembryomas [49]. They are diagnosed in younger women in a large scale. Younger patients with MOGCT prefer treatment that attempts to preserve ovarian function: 80% are less than 30 years of age and 70% to 75% have Stage I disease [50,51]. They tend to occur in young women and are usually unilateral. Bilateral involvement is extremely rare with the exception of dysgerminomas [23]. The emergence of new chemotherapeutics and the relatively younger age of onset of MOGCT lead to conservative surgery today which is convenient even in advanced stages for these tumours. According to the data in the literature, preserving the uterus and contralateral ovary is the ideal choice. Equal cure rates of bilateral or unilateral salpingo-oophorectomy have been reported in the literature [6, 48].

Sagae and Kudo detailed the surgical options in MOGCT cases according to the stage, histologic type and the patient's desire for fertility. They concluded that, for patients who require conservative surgery; USO is sufficient for patients with Stage IA dysgerminoma. Stage IB and IC patients must be treated with chemotherapy following USO. In patients with Stage I non-dysgerminoma, USO or USO plus chemotherapy is indicated for Stage IA immature teratoma grade I, and USO plus chemotherapy is indicated for Stage IA immature teratoma grade 2 or 3 and other histological types. USO plus chemotherapy or USO with contralateral partial ovariectomy plus chemotherapy is the ideal treatment for Stage IB, IC non-dysgerminoma. For patients with Stage II, III and IV of all histological types, conservative surgery consists of USO and a cytoreductive operation plus chemotherapy, followed by SLL or a second cytoreductive operation [49]. According to the majority of the authors, irrespective of histologic subtype and stage, conservative surgery should be the standard approach in the treatment of most malignant ovarian germ cell tumour patients [6, 23, 52].

Malignant ovarian germ cell tumors are now curable, mainly as a result of the great advances in chemotherapy in the past two decades. For all MOGCT patients except those of well-documented Stage IA pure dysgerminomas, postoperative chemotherapy is recommended. The generally recommended regimen for MOGCT is bleomycine, etoposite and cisplatin (BEP), which results in at least a 95% cure rate for early stage diseases and at least a 75% cure rate for advanced stages [18]. However, effects of chemotherapy on ovarian function, reproductive potential and fetal anomaly incidance remains to be enlightened.

Oncologic outcome

The effect of FSS in MOGCT on the oncologic outcome has been widely investigated. Zanetta *et al.* reported a series of 169 women with malignant germ cell ovarian tumours (70 dysgerminomas, 28 endodermal sinus tumours, 24 mixed tumours, and 47 immature teratomas). Seventy-one had advanced or recurrent disease. Fertility-sparing surgery was performed in 138 (81%) women: 88 of 98 (89%) women with Stage I tumour, nine of 14 (64%) with Stage II, 35 of 46 (76%) with Stage III, and four of six (66%) with recurrent tumour. Eighty-one patients received postoperative chemotherapy (73 platinum based and 8 non-plati-

num based). In this study survival rates were 94% for dysgerminoma, 89% for endodermal sinus tumour, 100% for mixed types, and 98% for immature teratoma. For women who were treated conservatively, the survival rates were 98%, 90%, 100%, and 100%, respectively [52].

Seventy-four FSS patients with malignant germ cell tumours were reviewed retrospectively by Low *et al.* [6]. In this study, there were 31 dysgerminomas (41.9%), 16 immature teratomas (21.6%), 13 endodermal sinus tumours (17.6%), 11 mixed germ cell tumors (14.9%), and three embryonal cell tumours (4.1%). There were 55 Stage I (75.7%), three Stage II (4.1%), 11 Stage III (14.9%), and four stage IV tumours (5.4%). Adjuvant chemotherapy was given to the 47 patients (63.5%). The overall mean follow-up period was 52.1 months. There were seven recurrences (9.5%) and two deaths (2.7%). Survival for patients with Stage I disease was 98.2%, compared to 94.4% in patients with advanced disease. Perrin *et al.* explained the results of 45 conservative surgery cases (44 USO and 1 cystectomy). Twenty-nine of all had chemotherapy. Five-year survival rate was found to be 97% for Stage I, and 87% for more advanced stages [23].

Thirty of 72 cases were operated on radically and the remaining 42 underwent conservative surgery in the report of Lira *et al.* Distribution of the histologic types were: 28 germ cell, 11 epithelial carcinomas and three undiagnosed forms. There was no significant difference regarding the disease-free survival period [53].

Reproductive outcome

Reproductive potential of FSS plus adjuvant chemotherapy is excellent. Zanetta *et al.* reported on 40 normal term pregnancies, six terminations, and nine miscarriages. In this study, four malformations were observed: one in 14 conceptions of patients who did not receive chemotherapy, and three in 41 conceptions of treated patients. Fertility seemed to be only marginally affected by chemotherapy. Miscarriages were in the expected range for the general population. The malformation rate was slightly higher than that of the general population, but no significant difference was seen between patients who received or did not receive chemotherapy [52].

In the study of Perrin *et al.*, amenorrhea was observed in 50% of patients who were treated with chemotherapy, but normal functions came back in 97%. Seven healthy neonates were delivered and no fetal anomalies were reported. None of the cases had permanent infertility [23].

In Lira's study, menstrual disorders were improved in six months for 89% of the cases. Cumulative pregnancy rate was 59%. Two recurrences were detected in cases with germ cell tumours [53]. In the study of Low *et al.*, during chemotherapy 61.7% of patients developed amenorrhea, but 91.5% of these resumed normal menstrual function on completion of chemotherapy. Fourteen healthy live births were achieved in the chemotherapy group and there were no documented birth defects [6]. Similar results are common in the literature clarifying the health of babies who were born after chemotherapy [2].

Impact of fertility therapy on the oncologic outcome after conservative surgery

It can be speculated that the fertility of patients undergoing FSS decreases due to the loss of at least one ovary, surgical adhesions and/or loss of ovarian function following adjuvant chemotherapy. But, it was clearly demonstrated that spontaneous pregnancy rates are satisfactory. The rate of spontaneous pregnancy among those attempting to conceive was found to be 60-88% in the literature [3, 4, 45]. However, these patients were usually not allowed to conceive spontaneously in the infertility clinics. The reason for this may be the anxiety of patients and clinicians to achieve pregnancy as soon as possible.

The relation between ovulation inducing agents and ovarian tumours is still an important question. As a first time Atlas *et al.* [54] attracted attention on that point of view and many reports have since been published [55]. The following trials investigated the relation between ovulation induction and ovarian tumours [55-57]. In a study performed on 3,837 patients Rossing *et al.* found four invasive and five borderline ovarian tumours, and reported an increased frequency of invasive and borderline ovarian tumour diagnosis when clomiphene citrate was given at 12 cycles or more [59]. Another prospective case-controlled study belongs to Potashnik consisting of 1,197 infertile patients who were followed-up 17.9 years. No significant difference was found between patients under fertility treatment and the controls [60]. Similar findings were noted in an Australian trial containing 10,358 individuals [61]. Shushan *et al.* reported an increased borderline ovarian tumour frequency in patients who were treated with human menopausal gonadotropin [62]. Additionally two cases were reported to occur following invitro fertilization (IVF) by Nijman *et al.* [63]. Dor et al found no correlation between number of IVF cycles or type of infertility and incidence of ovarian cancer [64].

The effect of ovulation induction therapy on behaviour of borderline tumours is still controversial [50]. Another point of importance here is the effect of ovulation induction on the recurrence of the ovarian malignancies. Although mentioned, there has been no report in the literature enlightening this issue [49, 65].

In a study of Benier *et al.*, 36 borderline ovarian tumour cases on infertility treatment following FSS were investigated. Seven of 36 (19%) patients who were not treated with IVF, and two of seven (29%) treated with IVF had recurrence later. There was no significant difference between two groups [44]. Although the follow-up period was as short as 49.7 months (3-110 months) it seems that the recurrence rate of borderline tumors is not affected by ovulation induction. Furthermore, Morice *et al.* reported one pregnancy following three cycles of clomiphene citrate treatment and another pregnancy following IVF following conservative treatment. No recurrence was observed [4]. In Morris *et al.'s* study, four cases of pregnancy occurred in 11 patients at child bearing age. Three of four pregnancies achieved by IVF and the remaining one were treated with ovulation induction. No relapse was reported [38].

Two cases have been reported that were treated with an IVF regimen after conservative therapy of borderline tumours. One of them was staged as IIIC borderline ovarian tumour and became pregnant after two cycles of IVF therapy and delivered successfully. The other individual was staged as IA borderline ovarian tumour and followed-up for three years. No recurrence was reported in either case [66].

Results of the studies on ovulation induction following FSS in the literature are difficult to compare because of different modes of treatment regimen, number of cycles, and follow-up duration. On the other hand, no data have been determined yet about increased prevalence of recurrence and fetal anomalies on ovulation induction after fertility-preserving surgery because of borderline ovarian tumours.

Adjuvant chemotherapy and ovarian function

The long-term effects of chemotherapy on ovarian function have been widely studied in patients treated for various malignancies such as Hodgkin's disease, gestational trophoblastic diseases, leukemia and breast carcinoma [67-69]. Effects of postoperative adjuvant chemotherapy on ovarian function differ according to cumulative drug dose, duration of therapy, different regimens of chemotherapy and patient age during treatment [70-72]. Prepubertal ovaries were shown to be more resistant to the adverse effects of chemotherapy [73].

The observed histologic changes in the ovaries of patients receiving chemotherapy include cortical fibrosis, reduction in number, and impaired maturation of follicles which lead to the increased serum gonadotropins and decreased serum estradiol levels [74,7]. In a study of Zanetta *et al.*, hypergonadotropic amenorrhea during treatment was seen in one (12.5%) of eight women who were treated with a doxorubicine and cyclophosphamide regimen, in 16 (76%) of 21 women who were on cisplatin, vinblastine and bleomycin, in 40 (95%) of 42 women who were treated with a weekly cisplatin, etoposide and bleomycin regimen, and in all six women who were treated with the three weekly cisplatin, etoposide and bleomycin regimen. They reported that irrespective of the type of regimen, median time to recovery of menstruation is highly correlated with the length of the treatment [52].

Assisted reproductive techniques in cancer patients

Assisted reproductive technology has opened a new page for future fertility of the cancer patients: embryo cryopreservation. Oocyte and ovarian cryopreservation remain experimental, but it is a technologic milestone for the future fertility of cancer patients.

The technique of embryo cryopreservation has evolved tremendously in the last few years and can offer a chance of fertility to women who have entered menopause following cancer treatment [7]. Cryopreservation of embryos can also be combined with surrogacy if the patient's uterus has been removed or if the patient has received radiation therapy to the pelvis [7].

Another novel approach is to obtain ovarian cortical tissue by laparoscopy using a newly designed apparatus to take five or six biopsies from the same ovary [76]. It can be performed within about 20 minutes and causes minimal bleeding, which is easily controlled. This technique allows a satisfactory collection of primordial ovarian follicles to cryopreserve. In this way, removal of the whole ovary can be avoided, as has been reported prior to chemotherapy in young women with Hodgkin's disease [77]. This approach potentially offers several advantages: it can be done very quickly without delaying cancer treatment; it does not necessitate controlled ovarian hyperstimulation (which may be contraindicated in some women with breast

cancer); and it can be performed on prepubertal girls. No successful pregnancy in humans has been reported by this technique so far [76] but transplantation of cryopreserved ovarian cortical tissue into castrated ewes was performed in 1994 and led to the conception and birth of lambs [78]. Thus, re-implantation of ovarian cortical strips into patients is likely to be accomplished in the future [79]. Particularly in ovarian cancer, however, one needs to be absolutely certain that there is no risk of re-implanting tumor cells. Many ethical questions also remain uncertain regarding the indications, risks, efficacy, and safety of this new approach [7].

Conclusion

Fertility saving surgery can be performed at all stages of borderline and germ cell tumours, but in invasive ovarian cancer it is limited to the early stages. Even if it is unavoidable to ectomise both of the ovaries, if possible, the uterus should be preserved. Following conservative surgery chemotherapy and ovulation induction can be applied safely. Radical surgery should be performed after completion of fertility except for germ cell tumours.

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