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Conservative management of epithelial ovarian cancer

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Summary

We are currently faced with a progressive delay in the age at which women conceive for the first time. This raises the possibility of the appearance of gynecologic disorders that may affect fertility, including neoplasms of the ovary. Fertility-sparing surgery is defined as the preservation of ovarian tissue in one or both adnexa and/or the uterus. Borderline ovarian tumor should be treated with conservative surgery. Salpingo-oophorectomy, or even ovarian cystectomy, are the procedures of choice, with recurrence rates of 2-3% and up to 20% if a simple cystectomy is performed. Cystectomy is indicated in patients with bilateral borderline tumors or in patients with a residual ovary. Borderline tumors with invasive peritoneal implants behave as an invasive cancer in 10-30% of cases with a survival rate of 10-66% compared with 100% in borderline tumors without invasive implants. Prophylactic oophorectomy is recommended when desire of conception has been accomplished. Conservative surgery in invasive epithelial ovarian cancer is limited to Stage IA, grade 1 tumor, and in some highly selected grade 2 tumors of serous, mucinous or endometrioid type, well-encapsulated and free of adhesions. The standard oncological surgical procedure with preservation of the uterus and normal appearing ovary is recommended. This includes salpingo-oophorectomy, excision of any suspicious peritoneal lesion, multiple peritoneal biopsies, appendectomy (particularly in mucinous tumors), and pelvic and paraaortic lymphadenectomy.

Key words: Ovarian cancer; Surgery of the ovary; Conservative surgery of ovarian cancer; Borderline ovarian tumor.

Introduction

Ovarian carcinoma, although less frequent than carcinoma of the cervix and endometrial carcinoma, causes a higher mortality than cervical and endometrial cancers together. This poor prognosis is related, among other factors, to the fact that most women with malignant tumors of the ovary are diagnosed in advanced stages of the disease. However, the increased use of ultrasound studies has been associated with a progressive increase in the number of cases in which diagnoses of malignancy are established at early stages as shown by the experience of our group [1] (Figure 1), as well as diagnoses at younger ages. This encouraged the possibility of a less radical and aggressive therapeutic approach, especially in women wishing to retain their fertility and, thus, being candidates for fertility-sparing surgery.

A review of the recent literature shows a movement towards supporting a clearly conservative approach that, in some cases, is only justified on the knowledge of a particular and novel technique. Without underestimating the great importance that any surgical advance may have in the field of gynecologic oncology, the objective of this report was to assess the role of fertility-sparing surgery in the treatment of ovarian carcinoma. It is important to take into account the aggressive and complex natural history of this condition, which makes it necessary to be extremely cautious in the selection of the type of surgery because surgical treatment is usually the first option, the efficacy of which is largely associated with the outcome of patients.

Definition of conservative surgery of epithelial ovarian cancer

Fertility-sparing surgery is defined as the preservation of ovarian tissue in one or both adnexa and/or the uterus.

All surgical procedures that are characteristic of surgical staging of ovarian carcinoma, such as total hysterectomy with bilateral salpingo-oophorectomy, appendectomy, omentectomy, peritoneal cytology, peritoneal and diaphragmatic biopsies, and pelvic and paraaortic lymphadenectomy should be considered individually for each indication of fertility-sparing surgery.

When the purpose of conservative surgery of epithelial ovarian cancer is the maintenance of fertility, then preservation of the uterus is indispensable, except in those countries in which gestational surrogacy (host uterus) is permitted by law. Therefore, the options available for preserving the uterus are as follows:

- Unilateral or bilateral cyst removal (cystectomy)
- Unilateral salpingo-oophorectomy
- Bilateral salpingo-oophorectomy; patient candidate for oocyte donation.

If the patient had undergone a hysterectomy before the development of epithelial ovarian cancer and wished to have children – a very exceptional case – only unilateral or bilateral cystectomy or unilateral oophorectomy may be considered because the patient would be a candidate for gestational surrogacy in which embryo transfer is expected to be performed with gametes from the genetic mother and father.

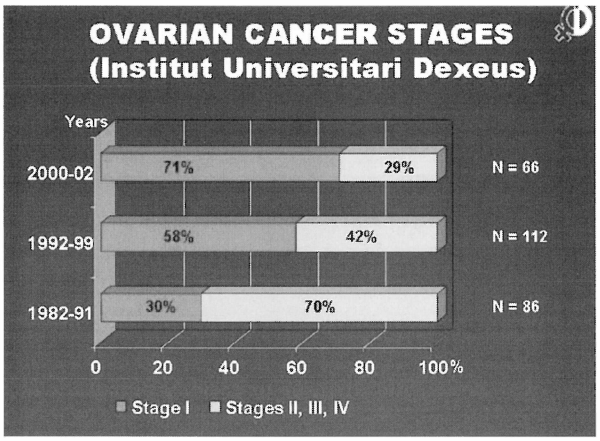

Figure 1. — Ovarian cancer stages from 1982 - 2002.

Indications

According to the International Federation of Gynecology and Obstetrics (FIGO) classification, conservative surgery may be indicated in the following cases:

- Borderline tumors
- Stage IA G1 tumors, and may be G2 tumors
- More controversial in Stage IB G1 tumors, although in recent reviews of the subject, this possibility is not accepted [2].

These indications obviously require careful considerations in each individual case and cannot be generalized. It should be noted that it is easy to establish theoretical guidelines, but in clinical practice, circumstances are very different. The diagnosis of an ovarian borderline tumor should be made on an intraoperative biopsy, which requires a lot of experience on the part of the pathologist and, even in this case, it is common that the intraoperative diagnosis may be different than the final diagnosis due to the presence of microinvasion or even invasive areas that were not seen at the initial microscopic examination.

Borderline ovarian tumors

Borderline tumors of low malignant potential are the less aggressive tumors of the ovary among the potential candidates for fertility-sparing surgery. According to epidemiological factors, some authors [3] consider that the epidemiologic features of women with borderline ovarian tumors are similar to those of women with epithelial ovarian cancer with the exception of an earlier age of onset. Most authors, however, recognize that borderline ovarian tumors represent a different biological process than invasive epithelial ovarian cancer [2, 4], and even taking into account the age of onset, invasive carcinomas show the same aggressive behavior in young women who have a 5-year survival rate similar to that quoted in the literature [5] independently of the age of the patients. When the course of borderline ovarian tumors with recurrence or progression of the disease is analyzed, a longer interval between diagnosis and progression as well as a higher survival rate [6] than that expected for invasive epithelial ovarian cancer can be observed.

Borderline tumors account for approximately 10-15% of all ovarian malignancies.

For any indication of fertility-sparing surgery, it is necessary to have an experienced pathologist available to define the characteristics of borderline tumors in the intraoperative biopsy specimen. Four histological features are essential:

- Papillary epithelial proliferation
- Atypical epithelial activity
- Mildly or moderately atypical nuclei
- Absence of stromal invasion

The absence of stromal invasion is a distinctive feature for the differential diagnosis with invasive ovarian carcinoma.

Peritoneal implants are found in 10-40% of cases of borderline ovarian tumors [2] and in 80% of cases, borderline tumors are not invasive [7]. A subtype designated *micropapillary serous carcinoma* is frequently accompanied by invasive implants and appears to behave as a low-grade invasive carcinoma [7], although recent studies have indicated that the micropapillary pattern alone does not imply an unfavorable prognosis [8].

The presence of different risk factors may affect the selection of surgical treatment, but in the majority of patients these factors are identified lately when decisions regarding the surgical procedure have already been made. DNA ploidy has been identified as a predictor of recurrence and survival, with good prognosis for DNA diploid tumors and DNA aneuploidy indicating high risk [9]. In a study of the prognostic significance of p53, Her-2, and EGFR oncogenes in borderline tumors [10], Her-2 and EGFR over-expression in combination, adjusted for age and p53, significantly improved the prognosis. In another study [11], the presence of aneusomy for chromosome 17 and HER-2 may predict tumor progression. The microsatellite instability caused by alterations in DNA repairing genes has been implicated in the pathogenesis of colon, endometrial, ovarian, and gastric carcinomas of hereditary nonpolyposis colorectal carcinoma, or Lynch syndrome. In a previous study by our group [12], six high-frequency microsatellite markers recommended by the National Cancer Institute [13] (BAT25, BAT26, NME1, D17S250, D5S346, and D2S123) were used to determine microsatellite instability in healthy and tumor tissue in each of 40 patients undergoing surgery for sporadic ovarian tumors. Our findings indicate that microsatellite instability lacks a significant role in the appearance or progression of sporadic ovarian tumors. In a recent review of 425 cases of borderline ovarian tumors collected from 26 hospitals in Spain (1990-1997) [14], it was shown that increased tumor markers are a risk factor for peritoneal implants, the same as tumor detection on ovarian surfaces and/or capsular rupture. In the multivariate analysis, peritoneal implants were the only independent predictor of recurrence (OR 5.68; 95% CI, 1.94 to 16.64).

Treatment

For more than 30 years reports of conservative treatment of borderline ovarian tumors have been published in the literature, with salpingo-oophorectomy and ovarian cystectomy for Stage I tumors, and a recurrence rate of 2.3% [15]. However, the most extended practice continues to be the standard treatment of total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, peritoneal cytology, and appendectomy.

Better knowledge of the natural history of borderline malignancies and the diagnosis of this type of tumor in young patients who have not completed childbearing and wish to preserve fertility potential, has allowed the basis of fertility-sparing surgery to be established. Although the diagnosis of an ovarian tumor of low malignant potential conveys a relatively benign prognosis, late recurrences after five to ten years of treatment have been reported [4]. Therefore, patients should take part in therapeutic decisions and be fully informed on the surgical strategy and eventual associated risks.

The risk of recurrence varies between 0% and 20% [9, 15, 16] and is higher if only an ovarian cystectomy has been performed. In a retrospective review of all women with borderline ovarian tumors diagnosed at Aberdeen, U.K. and Loannina, Greece between 1981-1993, conservative surgery for borderline tumors in young women permitted high conception rates, but recurrence of tumor was high in this group, 71%, and presented late [17]. Prolonged intensive follow-up is required for women treated conservatively for borderline malignant ovarian tumors.

Biopsy of the apparently unaffected gland has been proposed to reduce the risk of recurrence. However, this approach may be associated with infertility due to postsurgical adhesions or destruction of apparently healthy ovarian parenchyma. Taking into account the high rate of recurrence, *salpingo-oophorectomy* is the optimal treatment of unilateral borderline ovarian tumors. Ovarian *cystectomy* can only be performed in cases of bilateral tumors or in patients with a residual (solitary) ovary after a previous salpingo-oophorectomy. A second cystectomy may be proposed to preserve fertility in a previously treated patient with cystectomy, if recurrence of the borderline tumor in the residual ovary occurs. In a recent retrospective study of 17 patients treated with conservative management for a borderline ovarian tumor, undergoing unilateral salpingo-oophorectomy, unilateral cystectomy, or bilateral cystectomy, eight pregnancies were observed in seven patients in a median delay of eight months following the surgical procedure [18].

We believe that patients with suspicious adnexal tumors should be treated in referral centers, with the possibility of intraoperative biopsy and by specialized surgical teams in oncological surgery. In these conditions, current treatment of borderline ovarian tumors includes:

- Unilateral salpingo-oophorectomy (unilateral tumors) or salpingo-oophorectomy at the site of the largest tumor and contralateral cystectomy (bilateral tumors)
- Peritoneal cytology
- Multiple peritoneal biopsies
- Omentectomy
- Appendectomy (particularly indicated in mucinous tumors)

There is no consensus regarding surgical staging of ovarian serous borderline tumors, although a significant proportion of patients who undergo staging are noted to have extrapelvic spread [19, 20]. In a review of 200 patients with serous tumors of low malignant potential [21], the rate of recurrence after total hysterectomy with bilateral salpingo-oophorectomy was 3.7%, which increased to 8.1% after unilateral salpingo-oophorectomy and to 12.5% after cystectomy. Patients with intraperitoneal disease and negative lymph nodes showed a low incidence of recurrent neoplasm (5%), whereas the incidence of recurrence increased up to 50% when peritoneal implants and metastatic lymph nodes were considered all together. In this study, peritoneal washings, multiple peritoneal and diaphragmatic biopsies, omentectomy, pelvic and ipsilateral paraaortic lymphadenectomy (lymph node sampling) with intraoperative palpation of the contralateral lymphatic chain, and total or partial resection in case of involvement are recommended. On the other hand, it is well known that as a result of surgical staging up to 18% of patients with Stage I ovarian cancer are upstaged to Stage III. In our series, 14.4% of patients with ovarian cancer were upstaged after complete staging laparotomy [22]. These figures may support a routine staging lymphadenectomy, but it should be considered that lymph node involvement is usually referred to early stages of invasive ovarian cancer, a type of tumor with a natural history different than that of borderline tumor. It has been shown that in borderline ovarian tumors, lymphadenectomy is not associated with an improvement in the survival rates.

With regard to the surgical route, borderline ovarian tumors can be successfully treated through the laparoscopic approach. The percentage of recurrences in patients undergoing laparoscopy is similar to that of open surgery (20%) [23].

Serous borderline tumor of the ovary with *invasive peritoneal implants* merits special consideration because in 10-30% of cases, the biologic behavior is that of an invasive cancer [18, 23], with a survival rate of 10-66% [23, 24] compared with a nearly 100% survival rate for borderline tumors without invasive implants. Borderline ovarian tumors associated with invasive implants should be treated as patients with advanced ovarian cancer. However, the role of adjuvant chemotherapy in patients without residual macroscopic disease has not yet been elucidated [25].

In patients undergoing cystectomy in which the diagnosis of borderline ovarian tumor is established postoperatively, we consider that staging surgery is not indicated unless a thorough revision of the abdominopelvic cavity during the first operation was not performed. In case of reoperation, the laparoscopic approach would be the technique of choice.

Evidence of microinvasion is not associated with a worse prognosis when stromal invasion is 3 mm or less in depth and the area of invasion is < 10 mm^2 [26]. These arbitrary criteria, however, are difficult to define by the pathologist, particularly in the course of intraoperative biopsy.

Fertility after conservative treatment

There are numerous reports of spontaneous pregnancy after fertility-sparing surgery in patients with borderline tumors [2, 27, 28] with obstetric results similar to those of the general population. Despite fertility-sparing surgery, some patients may present secondary infertility which may require ovulation induction treatment. It has been speculated regarding the effect of fertility drugs on the development of borderline tumors. In a nationwide case-control study carried out in Israel [29] in which 164 invasive and 36 borderline epithelial ovarian tumors were analyzed, 11% of patients with invasive carcinoma and 22% of patients with borderline tumors reported that they had used hMG alone or in combination with clomiphene citrate. In our series of 33 patients [30], six patients had history of infertility, and an ovulation induction treatment had been performed in four of them (12%). However, a possible relationship between follicular stimulation and ovarian cancer has been excluded [31]. The adequacy of techniques for induction of ovulation in previously treated patients with borderline tumors has been questioned, but it has been shown that these techniques are safe and pregnancies are achieved without increasing the risk of recurrence.

In patients who undergo salpingo-oophorectomy with preservation of the uterus, oocyte donation and in vitro fertilization techniques will require hormone therapy to prepare the endometrium and maintain the pregnancy during the first months. There is no contraindication for in vitro fertilization and embryo-transfer treatment in these patients.

A controversial aspect is the need to perform salpingo-oophorectomy in patients who desire pregnancy after they have been able to conceive. Because the recurrence rate can be as high as 20%, routine oophorectomy would be unnecessary in 80% of cases. Therefore, if patients are well disciplined and the natural history of borderline tumors is taken into account, careful follow-up can be proposed, with oophorectomy postponed at ages close to menopause.

Invasive epithelial ovarian cancer

Between 3% and 7% of ovarian tumors are diagnosed before 40 years of age, and 7-8% of Stage I tumors are found in women under 35 years. In our series [1], a progressive increase of diagnoses in early stages of the disease as a result of the increasing use of ultrasound studies has been observed (Figure 1). Accordingly, the profile of younger patients who desire to preserve their reproductive function will become more frequent. However, this respectable desire should be carefully balanced by the gynecologist against any detriment to survival which is around 95% for Stage IA when the conventional radical surgical treatment is performed.

A review of data from patients with epithelial ovarian cancer treated with fertility-sparing surgery reported in the literature reveals that clinical series are heterogeneous, mostly because epithelial tumors are not individualized from other histologic subtypes. Candidates for fertility-sparing surgery should meet the following requirements:

- Disciplined patients as a guarantee of careful follow-up
- Serous, mucinous or endometrioid histologic type
- Well-encapsulated tumor and free of adhesions
- Stage IA, grade 1 and, in highly selected cases of grade 2 tumors

Some authors also include Stage IB, grade 1 and 2 tumors [33]. In our opinion, this indication is not acceptable even if conservative treatment is limited to preservation of the uterus. Patients undergoing this type of surgery should be recipients of oocyte donation, because the potential risks of the use of cryopreserved ovarian tissue from the neoplastic gland are unknown.

Fertility-sparing surgery applicable to Stages IA, grade 1 tumors and some highly selected grade 2 tumors should be the standard procedures, with preservation of the uterus and the apparently unaffected ovary, including:

- Salpingo-oophorectomy
- Omentectomy
- Excision of any suspicious peritoneal lesion
- Multiple peritoneal biopsies
- Appendectomy (particularly indicated in mucinous tumors)
- Pelvic and paraaortic lymphadenectomy

The degree of extension of lymphadenectomy is unclear. In the study of Benedetti-Panici *et al.* [33], contralateral lymphatic spread in a series of 35 patients with Stage I epithelial ovarian cancer was not observed. Other authors [34, 35] have found metastasis in the contralateral nodes, so that complete pelvic and paraaortic lymphadenectomy seems mandatory.

Biopsy of the residual ovary may induce secondary infertility and is not advisable especially when the ovary appears

normal to the surgeon [36, 37]. Microscopic implants in a clinically normal appearing ovary have been reported [38], but patients presented grade 3 histologic tumors, which in our opinion is a formal contraindication for conservative surgery.

Laparoscopic management of early ovarian cancer is safe and effective [39], although is poorly efficient in staging [40]. The outcome in terms of disease-free and overall survival does not seem to be affected when managing early ovarian cancers by laparoscopy or laparotomy [40].

In terms of survival, some authors have reported similar rates for conservative and radical surgery [37, 41]. However, in order to draw firm conclusions, the influence of histologic grade should be considered [42]. In the excellent study of Morice *et al.* [2], patients with Stage IA, grade 1 tumors showed a survival rate of 90%, which was comparable to the same figure obtained in patients undergoing radical surgery. Results, however, were notably worse when fertility-sparing surgery was used in Stage IA, grade 2 tumors. In these cases, disease-free survival was 66% compared with 75-95% in the group treated with radical surgery. All cases undergoing conservative surgery in stages higher than IA showed tumor recurrence with most relapses occurring in the residual ovary [36, 43].

Results regarding fertility are variable, probably in relation to the use of different fertility-sparing procedures. In one series [37], 25 pregnancies in 17 patients were obtained, although less favorable results have been reported by other authors [43]. Differences in pregnancy outcome may be related to the type of surgery used for restaging [2] which in the first series was performed through the laparoscopic route compared with laparotomy in the latter.

Conclusions

Fertility-sparing surgery is feasible in borderline ovarian tumors and shows excellent results in terms of fertility and survival. Patients with peritoneal implants may also be candidates for conservative surgery, although they should be fully informed and sufficiently disciplined to accept careful follow-up indefinitely. Preservation of the uterus and one ovary in patients with epithelial ovarian carcinoma requires an accurate and individualized assessment of each case, and should only be applied in serous, mucinous and endometrioid tumors, Stage IA, grade 1 tumors, and much more open to question in grade 2 tumors. Radical surgery should be recommended when the desire of conception has been accomplished. Ovulation induction treatment when necessary, is not contraindicated after fertility-sparing surgery.

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