

Fertility sparing options for women with ovarian neoplasms

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Abstract

Ovarian cancer is the leading cause of death by gynecological cancer and it is estimated that up to 17% of cases occur in women less than 40 years. In these patients it is often vital to maintain their fertility. This can be achieved using either fertility sparing types of surgery under strict selection criteria, or in combination with methods of assisted reproduction. In any case this should be avoided in patients over 40 years, and patients should be fully aware of the potential oncology and reproductive outcome. It is also needed a comprehensive surgical staging and patient's acceptance of a very close postoperative follow up. For patients with borderline tumor fertility sparing surgery is a safe option, with high percentages of achieved pregnancies and can be used either ovarian stimulation or ovarian tissue cryopreservation. In cases of invasive epithelial ovarian cancer fertility sparing clearly raises more concerns. The fertility surgery is recommended for patients

with stage IA and low risk factors and under strict conditions for stages IB and IC, but beyond it is not considered safe choice. After surgery, pregnancy can be achieved by natural conception or assisted reproduction. In recent years there is growing debate on in vitro maturation of oocytes and growth to maintain fertility, making it a promising alternative. Furthermore, cryopreservation of ovarian tissue is discussed and has found application in several experimental studies, but without sufficient data. In conclusion, we should mention that many methods are at an early stage and clinicians should always personalize each patient's treatment and provide full information about the chances of disease recurrence and the percentages of getting pregnant.

Key words: epithelial ovarian cancer; borderline ovarian tumor; fertility sparing; ovarian neoplasms

Every year about 200,000 new cases of ovarian cancer are diagnosed worldwide and 125,000 women die, even though the new chemotherapy regimens have greatly increased survival of patients with ovarian cancer¹.

Approximately 10% to 15% of epithelial ovarian cancers have histological features and biological behavior between benign tumor and invasive cancer and are called low - malignant - potential (borderline tumors). The epithelial ovarian cancer including borderline tumors is 90% - 95% of cases and the remaining malignancies are of only 5% - 10%². The cornerstone for the treatment of borderline tumors is the surgical removal. In cases of small size tumors the operation can be completed laparoscopically by experienced and well trained surgeons, or by classical laparotomic approach². In women of childbearing age who have a strong desire to preserve their fertility is acceptable to perform a single resection with preservation of the uterus and the contralateral adnexa³, even in cases where the final diagnosis is invasive cancer stage I FIGO.

It is estimated that 10% of epithelial cancers develop in young women under the age of 40². In these patients is often vital to maintain their fertility. This can be achieved using either fertility sparing surgery with strict patient selection criteria or in combination with methods of reproductive medicine.

Since the appearance of a tumor in the ovary, surgical removal and staging is necessary. The 1/3 of patients who appear to have disease in the ovary will be upstaged and will require postoperative chemotherapy. In patients with stage IA, IB grade 1 or 2, no further treatment is needed⁴. In this case, surgery can be performed in order to preserve fertility after selection of patients with strict criteria. Although the stage will increase in some patients, patients with stage I disease have excellent long - term survival after unilateral adnexectomy. Although in some cases chemotherapy is required, patients maintain their reproductive ability⁵.

Material and methods

For this literature review articles from the following electronic databases: pubmed, google scholar, Embase and Cochrane data base, have been used. The study also includes abstracts from international congresses and textbooks of Obstetrics - Gynecology, Gynecologic Oncology and Reproductive Medicine. In order to find the specific material we used the following keywords: epithelial ovarian cancer, Borderline ovarian tumors, fertility preservation, fertility sparing surgery and ovarian tissue cryopreservation.

The purpose of this literature review is the overall presentation of the available options to preserve fertility in cases of ovarian cancer. We introduce the already well - established fertility preservation techniques for some epithelial ovarian tumors, and new data from cases in recent years. Some are widely accepted and safe with adequate bibliographic data, while in other cases there are many controversies and doubts as a result of the small number of cases. We also report modern experimental techniques that are applied in cases of early stage ovarian cancer.

Preserving fertility in borderline tumors

Ovarian tissue cryopreservation is an excellent indication in borderline ovarian tumors, as this is a malignancy with excellent prognosis (5 - year survival of 99% for stage I) occurring in young women⁶. Until now, conservative surgery is the gold standard in treatment of early stages of borderline tumors without peritoneal implantations. Moreover, surgery is an adequate treatment and it is rarely required as adjuvant chemotherapy. In stage I of the disease the recurrence rate is 5 - 10% and 30 - 45% in patients that have done adnexectomy or cystectomy respectively⁷.

Conservative surgery for borderline tumors includes cystectomy or adnexectomy, peritoneal washings cytology, peritoneum biopsies, and where appropriate omentectomy and appendectomy⁸⁻⁹. Fertility sparing surgery was originally applied to early stages of the disease and did not significantly affect the survival rates¹⁰⁻¹². There were only higher rates of disease recurrence, suggesting the need for closer post-

operative follow up of these patients. Fortin et al¹³ reported ovarian stimulation in 30 patients with borderline tumor, after fertility sparing surgery, with a median follow up of 23 months. They concluded that it is safe to use fertility drugs in these cases.

When a relapse occurs in the residual ovary the best way to preserve fertility is cystectomy. However, in many cases this conservative surgery is not technically feasible, because recurrence is bulky and the position of relapse does not allow conservative surgery. Since the cystectomy is feasible (residual ovary size in situ good for fertility) this is the perfect choice for maintaining fertility^{7,14}. Many authors have reported spontaneous conception and similar approach exists for patients with bilateral tumors at initial treatment.

There is growing interest in exploring ways of improving the fertility of patients in which preoperative indications show that a fertility sparing surgery is not feasible. If the patient has a partner he can go through an emergency IVF procedure. After completion of the procedure a surgery with purpose to remove the entire ovary and preserve the uterus follows. Such cases have been described with successful results in the literature^{13,15}. Nevertheless, the safety of such an approach is very strongly doubted. Moreover, such a treatment can not be recommended in patients without a partner.

In such cases, another option is cryopreservation of ovarian tissue. But so far there are not enough publications with ovarian tissue cryopreservation in patients with borderline tumors. One explanation for this is the reluctance of several research groups to date to suggest such an option for treating an ovarian tumor. The tumor is located in the organ which will be maintained raising many questions regarding safety and possible recurrence of the disease with re-implantation of cells in the future re-implantation of ovarian tissue sections. The risk of developing disease in cryopreserved tissue is extremely low in macroscopically normal ovarian tissue. The presence of microscopic disease in the contralateral ovary is low and Morice et al¹⁶ reported that their initial experience in 14 patients showed no microscopic disease after tumor malignancy in the contralateral ova-

ry. No patients experienced tumor cells in the part examined. However, the probability of cancer cells is increased in cases of serous papillary borderline tumor and in advanced stage disease.

Fain - Kahn et al¹⁷ reported that in borderline tumors cryopreservation of ovarian tissue is feasible in 53%. The pregnancy rate after fertility sparing surgery ranged from 32% to 100%¹⁸⁻¹⁹. Table 1 shows the pregnancy rates reported in the literature after conservative treatment of borderline ovarian tumors. The conception was either automatic or subsequent IVF.

Other researchers have developed other techniques to avoid the risk of transmitting cancer cells from cryopreserved ovarian tissue. Conducting in vitro maturation (IVM) and follicular isolation is one option. IVM has been successful in one 43 years old patient with a borderline tumor²⁰, but with low numbers of oocytes.

Where it is feasible to carry out cystectomy, there is no need for cryopreservation, as conservative surgery is considered the best option for preserving fertility. Furthermore, removal of ovarian tissue may result in infertility. Another reason for making cryopreservation is to find malignant recurrence in patients with a history of mucous borderline tumor. In these few common cases cryopreservation of ovarian tissue is recommended. We should also mention that technical reasons during the surgery may not allow adequate tissue retrieval for cryopreservation, especially when the ovary is occupied entirely by tumor.

The next step in maintaining fertility in borderline tumors is to determine the minimum volume of residual ovarian tissue for freezing that is required to achieve the sufficient number of follicles thawing. In contrast there is a limitation of the potential existence of infiltration when taking the most of the ovaries⁶.

Fertility preservation in epithelial ovarian cancer

The increase in early gynecological control using ultrasound resulted in increased diagnosis of ovarian cancer at an early stage. Also, most women give birth to their first child in an older age, so the need for pre-

servicing fertility after diagnosis of early - stage ovarian cancer is growing. 3 - 17% of all epithelial ovarian cancers and 25% of stage I are in women under 40 years old^{21, 22}.

The surgery to maintain fertility is more aggressive than a simple unilateral adnexectomy. There is always risk of postoperative pelvic adhesions with potential to cause infertility. However, there are reports that there is no difference in the pregnancy rate²³.

For patients with disease beyond stage IC fertility preservation is not considered as a safe option and should not be attempted. Park et al²⁴ reported 3 cases of patients with disease stage II and III which died from the disease 10 and 16 months respectively after the initial treatment.

Adjuvant chemotherapy in patients with stage I disease is necessary in unusual cell types with poor differentiation and stage IC^{25, 26}. The adjuvant chemotherapy is therefore an important factor of treatment to preserve fertility but should be added only in patients with high risk factors.

Morice et al²⁷ reported 33 patients with stage I disease who underwent unilateral adnexectomy. There were 11 recurrences of which 7/30 (23%) were stage IA and 3/3 (100%) IC. For this reason they do not recommend making adnexectomy in stage bigger than IA. However, the number of patients with IC disease or IA/G3 was too small to draw reliable conclusions. Worth mentioning is the fact that in 3 patients the relapses were in remote areas without any disease in the remaining ovary.

Instead, Schilder et al⁵ reported 42 cases of stage IA and 10 of stage IC which underwent fertility sparing surgery in 8 different centers. There was one recurrence in 10 patients (10%) with stage IC. Moreover, Zanetta et al²⁸ in a series of 22 stage IC cases found one relapse (1/22, 4.5%) in the pelvic area and recommend fertility sparing surgery even for patients with stage IC. In another study, Kajiyama et al²³ did not report any difference in overall survival and disease-free survival among patients with stage IA and IC.

The fertility sparing surgery in patients with stage IB disease is extremely rare. If it is desired to maintain

the contralateral ovary at this stage is necessary to remove the tumor from the ovarian tissue with partial resection. However, it may remain in the tumor cells in the residual ovary, despite the intraoperative macroscopic and microscopic examination. Kajiyama et al²³ reported a case of recurrence and death from peritoneal carcinomatosis after a long time. Unlike, Park et al²⁴ reported two cases of patients without any evidence of recurrence, while Colombo et al²⁹ and Zanetta et al²⁸ reported each one case without any evidence of recurrence. Since the number of cases is too small it is very difficult to draw conclusions about safety at this stage of the disease. The fertility sparing surgery can be considered safe when there is a good portion of ovarian tissue remaining²⁴. Though, we always have to keep in mind the possible increased risk of disease recurrence.

The selection of patients for fertility preservation is based largely on the stage of disease. For this reason a complete surgical staging is needed. Up to 30% of patients with presumed early stage disease were up staged after thorough staging surgery, due to microscopic metastases in the peritoneal washings, lymph nodes, omentum or the diaphragm³⁰. If the patient is not completely staged, this is a negative prognostic factor³¹, while complete staging is necessary to avoid possible adjuvant chemotherapy.

The standard procedure involves pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal washings cytology, multiple peritoneal biopsies and possibly appendectomy. There are several controversies about the necessity of lymphadenectomy and appendectomy. The incidence of pelvic and para-aortic lymph node metastases is 8 - 30% in an apparent early stage^{30, 32}. Cass et al³³ found that 21% of patients with pelvic or para-aortic lymph node metastases were found on the opposite side from that which was the original disease. These data demonstrate the necessity of systematic lymphadenectomy in the staging surgery^{34, 35}. The appendectomy in the early stage of disease and non-mucous tumors offers no proven benefit in many centers is still optional^{24, 36}.

Table 1. Fertility sparing in women with borderline ovarian tumor

	Number of patients	FIGO Stage	Fertility outcome (number of patients that achieved pregnancy)	Cancer recurrence rate
Zanetta et al, 2001 ³	184	I - III	44	28/184 (15%)
Morice et al, 2001 ¹⁶	49	I - III	16	9/49 (18%)
Fauvet et al, 2005 ¹⁰	162	I - III	30	27/152 (17%)

Table 2. Fertility sparing in women with epithelial ovarian cancer

	Number of patients	FIGO Stage	Grade	Fertility outcome (number of patients that achieved pregnancy)	Cancer recurrence rate
Zanetta et al, 1997 ²⁸	56	IA - IC	G1 - G3	27	5/56 (9%)
Morice et al, 2000 ²⁷	25	IA - IC	G1 - G3	4	7/25 (28%)
Schilder et al, 2001 ⁵	52	IA - IC	G1 - G3	31	5/52 (10%)
Schlaert et al, 2009 ³⁸	20	IA - IC	G1 - G3	9	3/20 (15%)
Sato et al, 2010 ⁴²	211	IA - IC	G1 - G3	76	12/21 (9%)
Kajiyama et al, 2010 ²³	60	IA - IC	G1 - G3	13	8/60 (13%)

Another controversial point is how to evaluate the contralateral ovary. Munnell et al⁶ calculated that the probability of a hidden disease in macroscopically normal ovary is 12%. Moreover, Benjamin et al³⁷ reported a 2.5% presence of microscopic disease in the contralateral ovary. Schlaerth et al³⁸ evaluated the contralateral ovary macroscopically with wedge biopsy and cystectomy and found no infiltration of the contralateral ovary in 20 cases. Also Colombo et al²⁹ and Zanetta et al²⁸ by performing a biopsy of the contralateral ovary did not find any disease.

An important issue that has been reported is the possibility of infertility and ovarian failure after a wedge biopsy¹⁶. Overall, however, careful inspection and biopsy of the contralateral ovary is considered adequate and safe procedure.

The evaluation of the endometrium is another important parameter to diagnose a hidden disease. There is always the possibility of synchronous endo-

metrial cancer or extension of ovarian cancer in the endometrium, especially in cases of endometrioid ovarian cancer. For this reason, it is recommended endometrial biopsy during the surgical staging, especially in patients with endometrioid ovarian cancer. Park et al²⁴ reported that in 8 cases of endometrioid tumor, endometrial cancer cells were not found in any case, while Schlaerth et al³⁸ in 14 cases found no development of carcinoma at the time of surgery, but one patient developed endometrial cancer 15 months after surgery. Zaino et al³⁹ found coexistence of endometrial cancer in endometrioid carcinomas at a rate of 10%. Therefore endometrial biopsy is recommended as part of the fertility sparing surgery.

The histologic grade (differentiation) is another prognostic factor in an early stage disease³¹. Fertility preservation is considered safe only in cases of grade I and II and not grade III, even if it is stage IA that will receive chemotherapy. The histological type is also

an important prognostic factor⁶. Park et al²⁴ reported 4 patients with clear cell ovarian cancer, of which 2 (stage IA) relapsed and died from the disease. For this reason fertility sparing surgery is not recommended in such aggressive histological types⁶.

Another important controversy is whether after completion of the childbearing (or after the age of 40 years) a total hysterectomy and adnexectomy must be performed. The decision should be individualized for each patient, taking into account all prognostic factors; considering that the possibility of late recurrence is not negligible. Morice et al²⁷ mentioned the latest relapse after more than 10 years. It is necessary to follow up closely these patients every 3 months for the first 2 years and then every 6 months. The check should include ultrasonography and tumor markers. Several researchers recommend delaying radical surgery to menopause as a logical decision^{24,40}.

In addition fertility preservation by preserving the uterus and the adnexa has non-reproductive benefits. A recent meta-analysis showed risk reduction for cardiovascular diseases⁴¹.

Table 2 shows the articles with achieved pregnancies. Satoh et al⁴² reported the biggest number of patients so far (211), with 76 achieved pregnancies. Park et al²⁴ mentioned that all 62 patients had menstruation after surgery while most patients who achieved pregnancy they did it without any birth defect, despite the increased proportion of patients receiving chemotherapy. Also Schlaerth et al³⁸ reported 6 patients that achieved pregnancies.

The ovarian tissue cryopreservation as an alternative to preserve fertility is still an experimental procedure. There are no data yet for firm conclusions, only a few report describing the application of the method in epithelial ovarian cancer⁴³.

Conclusion

Preserving fertility in patients with ovarian tumor should be performed with strict criteria selection of patients, based on the histological type of disease and prognostic factors. In any case this should be avoided in patients over 40 years and patients should be fully

aware of the potential oncological and reproductive outcome. Also it is necessary a comprehensive surgical staging and the patient's acceptance of a very close postoperative follow up.

For patients with borderline tumor fertility sparing surgery is a safe option. It is quite common to achieve a pregnancy after natural conception, and more rarely may require ovarian stimulation and IVF. Another alternative with very encouraging results is the cryopreservation of ovarian tissue and use it thereafter.

For invasive epithelial ovarian cancer fertility preservation clearly raises more concerns. Fertility preservation surgery is recommended for patients with stage IA and low risk factors and under strict conditions for stages IB and IC, but not beyond what is considered a safe choice. After surgery, pregnancy can be achieved by natural conception or assisted reproduction. The use of drugs for stimulation is also highly questionable. In recent years there is growing debate on in vitro maturation of oocytes and development to maintain fertility, making it a promising alternative. Furthermore, cryopreservation of ovarian tissue is discussed and has found application in several experimental studies, but without sufficient data. Main concern is the re-implantation of cancer cells and the direction of researchers is to find a safe method of screening for potential tumor cells. There are also prospects for the use of cryopreserved ovarian tissue to obtain oocytes for further use in the reproductive process.

We must always keep in mind that all these methods are at an early stage and we should always personalize the treatment of each patient. In addition the patient should be fully informed of the chances of disease recurrence and the pregnancy rates. ■

Conflict of interest

All authors declare no conflict of interest.

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