Fertility preservation in ovarian cancer

This article aims to access feasibility and safety of fertility-sparing surgery in women with germ cell malignancies, low malignant potential tumors and early-stage epithelial ovarian cancer who desire to preserve reproductive function. Current data suggest that fertility-sparing surgeries are safe and have promising reproductive outcomes. Cryopreservation has emerged as a fertility preservation option and consists of various forms, including embryo, oocyte and ovarian tissue cryopreservation. Fertility-sparing surgeries for women with early-stage malignancies have proven efficacy in preserving fertility without apparent adverse impact on cancer outcomes. Advances in assisted reproductive technologies have provided patients with more fertility options.

KEYWORDS: cryopreservation ■ early-stage ovarian cancer ■ fertility-sparing surgery

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With 21,650 new cases every year, ovarian cancer is currently the fifth leading cause of death from all cancers in women in the USA [1]. Among gynecological cancers, it is the leading cause of death, typically presenting with stage III/IV disease. At present, 12.2% of ovarian cancers occur in women younger than 40 years of age [2]. Most of these cases are tumors of low malignant potential, malignant germ cell tumors and early-stage invasive epithelial cancer.

Recent advances in diagnostic tools have led to earlier detection of ovarian cancer. Approximately one quarter of new cases of ovarian cancer are classified as stage I, with excellent 5-year survival rates of over 90% [2]. Owing to increased survival, there is a new focus on the quality of life in cancer patients.

Among quality-of-life factors in cancer survivors, fertility preservation in premenopausal women is a high priority. A study by Wenzel *et al.* reported that survivors of lymphoma, gestational trophoblastic tumor and cervical cancer who were unable to have children after cancer treatment, but who still desired fertility, experienced significant regret [3].

Various fertility-sparing options are now available for women with ovarian cancer, especially in patients with early-stage disease. More conservative surgeries are often seen as the standard of care for some types of ovarian cancer. Emerging technologies, such as embryo, oocyte or ovarian tissue cryopreservation and transplantation, are continuing to evolve as potentially viable options for future fertility for women with ovarian cancer.

Low malignant potential tumors

Low malignant potential tumors (LMPTs) or borderline ovarian tumors represent approximately 15% of ovarian cancers [2]. Approximately 30% of LMPTs occur in women younger than 40 years of age [4], and are predominantly stage I at diagnosis (82%) with survival of 99% at 5 years [2]. However, recurrences can occur even more than 10 years after diagnosis. These tumors are epithelial in origin but lack definitive stromal invasion. The most common histological type is serous, followed by mucinous [2]. Serous LMPTs are bilateral in 30% of cases and associated with extraovarian lesions in over 30% of cases. The metastatic potential of LMPTs is relatively low and the recurrence rate is 2.1% with long disease-free intervals. Although the prognosis of patients with disease limited to the ovary is excellent, the outcome of patients with disease that is not limited to the ovary is variable.

Surgical removal of the tumor is the most important intervention in the management of LMPTs. However, the extent of surgery, including the role of staging procedure, continues to be defined. The mean age for LMPT presentation falls within the childbearing period; therefore, fertility-sparing surgery is a very important issue. Proposed conservative surgical procedures for LMPTs involve conservation of the uterus and salvaging at least a portion of one ovary, and include unilateral adnexectomy, unilateral adnexectomy and contralateral cystectomy, unilateral cystectomy and bilateral cystectomy. Fertility preservation, including unilateral salpingo-oophorectomy or ovarian cystectomy,

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has demonstrated feasibility with over 10 years of follow-up in early-stage disease. However, in young patients with advanced-stage disease (extraovarian spread) the safety of conservative management remains unclear [5]. There are a very limited number of studies that have reported on the fertility outcome of conservatively treated cases. In addition, 30% of patients with LMPTs have pre-existent infertility and the use of infertility drugs in patients with a high risk of recurrence continues to be a potential concern.

Guidelines for the surgical treatment of LMPTs are similar to those of ovarian cancer, and in women who do not have a desire for future fertility this includes peritoneal washings, hysterectomy with bilateral salpingo-oophorectomy (BSO) and staging, including omentectomy, multiple peritoneal biopsies, lymph node sampling and appendectomy for mucinous tumors. Conservative surgery is complicated by a higher rate of relapse. In a recent large retrospective study, De Iaco *et al.* compared the outcome of 168 women who had fertility-sparing surgery – cystectomy or unilateral salpingo-oophorectomy – with radical surgery, which included BSO with or without total hysterectomy [6]. As in prior studies, the rate of recurrence was highest in the cystectomy group (34%) compared with unilateral salpingo-oophorectomy (20%) or the radical group (6%). However, in this study, none of the relapsed patients died of the disease, which confirmed previous reports indicating that recurrences after fertility-sparing surgery are generally characterized by excellent long-term survival [7]. Recurrences after cystectomy can occur ipsilaterally or contralaterally, but such recurrences may not affect overall survival. Given the risk of recurrence, cystectomy should only be considered in young patients with bilateral tumors or a previous history of unilateral adnexectomy.

Table 1 summarizes several studies that have demonstrated successful pregnancies after treatment of ovarian tumors of low malignant potential. In combining the results in the studies from Table 1, 21% of all the patients that underwent fertility-sparing surgery became pregnant. Of the studies that reported the number of patients who attempted to conceive, 52% of these patients successfully became pregnant at least once. This confirms that conservative treatment can preserve fertility and it is an acceptable option for women who desire fertility preservation. The majority of the published conservative surgeries for LMPTs are stage IA–II, although there is also evidence to support this type of surgery in advanced-stage LMPT. A recent French study focused on the more challenging group of LMPTs, and limited the study to only advanced-stage serous LMPTs. The study looked at 162 women with advanced-stage serous LMPTs who received conservative treatment. A total of 18 pregnancies (nine spontaneous) were observed in 14 patients [8]. This study demonstrates that spontaneous pregnancies can be achieved after conservative treatment even in advanced-stage borderline ovarian tumors (with noninvasive implants) but the recurrence rate is high; however, this high rate had no apparent impact on survival.

Germ cell malignancies

Malignant ovarian germ cell tumors comprise approximately 5% of all ovarian malignancies. Germ cell malignancies are most common in younger women: 83% of cases occur in women under the age of 40 years, often in women in their teens and twenties. Owing to the high rate of incidence in young women, the preservation of fertility is an important aspect in the management of these tumors. These malignancies constitute a broad range, including dysgerminoma (30–40%), immature teratoma, endodermal

Table 1. Ovarian low malignant potential tumors: pregnancies after fertility-sparing surgery.

Study (year)	Patients (n)	Stage	Pregnancies (n)	Patients who conceived (n)	Patients who attempted to conceive (n)	Conception rate (%)	Ref.
Morris *et al.* (2000)	43	IA–III	25	12	24	27.91	[48]
Zanetta *et al.* (2001)	189	IA–III	41	44	NR	23.28	[49]
Morice *et al.* (2001)	44	IA–III	17	14	NR	31.82	[50]
Camatte *et al.* (2002)	17	II–III	8	7	9	41.18	[51]
Fauvet *et al.* (2005)	162	IA–III	30	21	65	12.96	[8]
Park *et al.* (2009)	184	IA–III	33	27	31	14.67	[52]
Uzan *et al.* (2009)	41	II–III	18	14	NR	34.15	[53]
All studies	680		172	139		20.44	

NR: Not recorded.

Table 2. Ovarian granulosa cell tumors: pregnancies after fertility-sparing surgery.

Study (year)	Patients (n)	Stage	Pregnancies (n)	Patients who conceived (n)	Patients who attempted to conceive (n)	Conception rate (%)	Ref.
Low *et al.* (2000)	74	IA–IV	16	19	20	25.68	[54]
Zanetta *et al.* (2001)	138	IA–IC	55	28	32	20.29	[55]
Tangir *et al.* (2003)	64	IA–IV	47	29	38	45.31	[12]
Zanagnolo *et al.* (2004)	39	IA–IC	11	36	NR	92.31	[56]
Nishio *et al.* (2006)	30	IA–IV	4	8	12	26.67	[11]
Chan *et al.* (2008)	313	IA–IV	NR	29	38	9.27	[57]
All studies	658		133	149		22.64	

NR: Not recorded.

sinus tumor, embryonal carcinoma, ovarian choriocarcinoma, polyembryoma and mixed (dysgerminoma plus endodermal sinus tumor). For these malignancies, fertility-sparing surgery, in which at least one ovary and the uterus are spared, is the current standard of care [9].

Conservative surgery combined with chemotherapy is an acceptable option for these patients. For those patients who require postoperative chemotherapy, the standard therapy includes the combination of bleomycin, etoposide and cisplatin. If chemotherapy is administered, there is a risk of ovarian failure in 20–30% of patients [10]. Although premature menopause may occur, approximately 80% of those who undergo fertility-sparing surgery and chemotherapy may expect to preserve reproductive function. Table 2 shows several series documenting successful pregnancies in malignant ovarian germ cell tumors. Nishio *et al.* published a recent study in Japan involving 35 patients, 30 of whom underwent conservative surgery, as five of them had stage III and IV disease and, therefore, received radical surgery. Of the 30 patients who underwent conservative therapy, 12 attempted to conceive and eight achieved at least one pregnancy [11]. In an earlier study, one of the largest series, Tangir *et al.* followed 64 patients for a median of 122 months. Of the 38 patients who attempted to conceive, 29 achieved at least one pregnancy (76%). Of the ten patients with stage III disease who attempted to conceive, eight were successful [12]. These data suggest that conservative management can be considered for women with malignant ovarian germ cell tumors even when diagnosed at advanced stages.

Epithelial ovarian carcinoma

Epithelial ovarian carcinomas (EOC) are relatively rare in the reproductive age group. Only 10% of patients with EOC are younger than 40 years of age, and only 3–4% are younger than 30 years of age. These types of cancers are much more aggressive than tumors of low malignant potential or germ cell malignancies. Therefore, standard treatment for patients with epithelial ovarian cancer consists of total abdominal hysterectomy, BSO, omentectomy, tumor debulking, pelvic and para-aortic lymphadenectomy, multiple biopsies and peritoneal washings. Most cases are followed by adjuvant platinum-based chemotherapy. Approximately 25% of tumors are stage I, and this early-stage disease is associated with a 5-year survival rate approaching 90% [13].

Given the excellent 5-year survival rate in women with early-stage invasive EOC, factors related to quality of life are very important. Although relevant to only a minority of ovarian cancer patients, fertility preservation is a significant quality-of-life concern for those desirous of future childbearing. Furthermore, there has been a recent increase in early gynecologic check-ups using ultrasonography, which has increased the frequency of epithelial ovarian cancer diagnosis at earlier stages. In addition, there has been a trend toward women giving birth to their first child at an older age. Therefore, the diagnosis of EOC during reproductive years has become more frequent and the demand for fertility-sparing surgery in early-stage EOC is increasing.

Fertility-sparing surgery has been proposed to be limited to stages IA–IC. Complete surgical staging is necessary to ensure a proper selection of stage I patients who want to preserve fertility. Table 3 shows six studies with an aggregate of 98 pregnancies in 66 women, with 22 recurrences in 215 patients. Most were stage I, but these included those up to stage III. When comparing conservative treatment with radical surgery, the series by Zanetta *et al.*, Schilder *et al.*, Raspagliesi *et al.* and Anchezar *et al.* (Table 3) show no significant difference in early-stage patients with well-differentiated tumors. Based on the studies in Table 3, conservative surgery can

Table 3. Ovarian epithelial carcinomas: pregnancies after fertility-sparing surgery.

Study (year)	Patients (n)	Stage	Pregnancies (n)	Patients who conceived (n)	Patients who attempted to conceive (n)	Conception rate (%)	Ref.
Zanetta *et al.* (1997)	56	IA–II	17	20	NR	35.71	[18]
Morice *et al.* (2001)	25	IA–II	3	4	4	16.00	[58]
Schilder *et al.* (2002)	52	IA–IC	26	17	24	32.69	[59]
Morice *et al.* (2005)	34	IA–IC	10	9	NR	26.47	[14]
Anchezar *et al.* (2009)	18	IA–IIIB	7	6	7	33.33	[19]
Schlaerth *et al.* (2009)	20	IA, IC	9	6	NR	30.00	[60]
Park *et al.* (2008)	62	IA–IIIC	22	15	19	24.19	[15]
Raspagliesi *et al.* (1997)	10	IA–IIIC	2	3	5	30.00	[61]
Borgfeldt *et al.* (2007)	23	IA–IC	30	15	NR	65.22	[4]
Kwon *et al.* (2009)	21	IA, IC	5	5	NR	23.81	[62]
All studies	321		131	100		31.15	

NR: Not recorded.

be considered in young women with intraoperative findings of unilateral involvement with capsule intact (stage IA) and low-grade disease who undergo complete surgical staging. The opposite ovary and uterus are thus spared assuming they appear grossly disease-free.

Although Table 3 includes some studies with stage II or stage III disease, based on the results of these studies there is controversy pertaining to whether conservative treatment is feasible in patients with higher than stage IA disease. For example, Morice *et al.* reported 11 recurrences in 34 patients with stage IA–IIA disease who underwent conservative surgery. All recurrences occurred in patients with greater than stage IA disease. Therefore, the authors concluded that fertility-sparing surgery should be reserved for patients with stage IA disease [14]. In a more recent study, the largest case series of conservative fertility-sparing surgery for EOC by Park *et al.*, the 5-year disease-free survival (DFS) and overall survival of patients with stage IA disease were 83 and 91%, respectively, and the 5-year DFS and overall survival of patients with stage IC disease were 78 and 88%, respectively. These were comparable to the survival rates of patients with stages IA and IC treated with more radical surgery [15]. This study suggests that fertility-sparing surgery could be considered, even for women with stage IC EOC.

In analyzing the combined results of the studies in Table 3, conservative surgery may be safe for women with stage IB EOC if an adequate portion of the normal ovary can be preserved, but fertility-sparing surgery should not be performed in patients with disease staged higher than IC. In the study by Park *et al.*, of the three patients who were upstaged to stages II and III due to microscopic metastatic disease, two had tumor recurrences and died of disease 10 and 16 months after initial treatment [15]. In examining women with stage I disease, we can also conclude from these series that conservative treatment should not be recommended for patients with grade 3 disease, even in those with stage IA tumors who receive adjuvant chemotherapy. Histologic type is also an important prognostic factor in early-stage EOC, in that patients with clear-cell carcinoma have a lower survival rate than those with serous, mucinous and endometrioid tumors. In the Park *et al.* study, only four patients had clear-cell carcinoma, but two with stage IA had recurrence and one died [15]. Therefore, fertility-sparing surgery cannot be recommended in patients with such aggressive tumor types.

In comparing the recurrence of the patients in the six studies with and without high-risk factors, if conservative surgery is being used for the purpose of future fertility, then adjuvant chemotherapy after conservative surgery should only be administered to patients with high-risk factors. However, careful post-therapy surveillance, including ultrasonography and assessment of tumor markers, is mandatory every 3 months for 2 years, then every 6 months thereafter.

One of the dangers of conservative treatment is the risk of microinvasive carcinoma in the remaining ovary. The role of wedge biopsy of the remaining grossly normal-appearing ovary is controversial. Munnell estimated the risk of occult disease on the grossly normal-appearing ovary to be 12% [16]. Benjamin *et al.* found that only three out of 118 patients (2.5%) with normal-appearing contralateral ovaries had microscopic occult disease at the time of BSO [17]. In Zanetta *et al.* and Anchezar *et al.*, none of

the patients with macroscopically normal ovaries had microscopic metastasis [18,19]. Routine biopsies of the contralateral ovary have been recommended, but based on these recent studies, this procedure should be limited to patients with suspicious lesions in the remaining ovary. In addition, it has been reported that wedge biopsy can cause mechanical infertility or even ovarian failure. Although more recent reports have found that none of the patients who underwent fertility-sparing surgery had microscopic metastases in the normal-appearing contralateral ovary, careful inspection of ovarian surfaces and biopsies of suspicious lesions or cysts is recommended. In the study by Park *et al.*, of the nine patients who underwent cystectomies for benign-appearing cysts of the contralateral ovary, two had ovarian cancer [15].

In discussing the newer trends toward fertility-sparing surgery for early invasive ovarian cancer, the use of laparoscopy should not be ignored. Laparoscopic fertility-sparing staging of early ovarian malignancies improves postoperative outcomes, such as pain, hospital stay, complication rates and aesthetic results. There have been several recent studies that have demonstrated that in specific patients the performance of comprehensive laparoscopic surgical staging of ovarian cancer is as sage and efficacious as surgical staging performed by laparotomy when conducted by a gynecological oncologist with training in laproscopic procedures [20–22].

Another current debate is the value of completion hysterectomy with adnexectomy after childbearing is completed. Many authors advocate definitive total abdominal hysterectomy and BSO after completion of childbearing, unless the disease-free interval is long. In reviewing the studies in Table 3, most patients had long-term DFS without radical surgery, and the 5- and 10-year DFS and overall survival rates were identical in most series. Therefore, these series suggest that observation or delaying radical surgery until after menopause may be a reasonable option. Another goal of fertility-sparing surgery is the preservation of the endocrine function of the remaining ovary, not just the ability to bear children.

Special considerations should be taken for *BRCA1*/*BRCA2*-positive patients; therefore, genetic testing and counseling can be very helpful in planning future treatment. *BRCA1* mutation carriers have a 20–50% lifetime risk of ovarian cancer, and *BRCA2* have a 15–20% risk. Screening recommendations for these women include transvaginal ultrasound and cancer antigen 125 either semiannually or annually beginning at the age of 25–35 years, but once childbearing is complete, prophylactic BSO is recommended [23]. This clear evidence suggests that prophylactic surgery is a risk-reducing intervention that can alter the natural history of inherited predispositions (i.e., *BRCA1*/*BRCA2* germline mutations). The Society of Gynecologic Oncology (SGO) published guidelines in 2007 to help the medical community identify women who would benefit from hereditary cancer risk assessment [24]. The SGO Education Resource Panel for Hereditary Cancers believes that individuals with a personal risk of having an inherited predisposition to cancer of greater than approximately 20–25% should undergo genetic risk assessment. For hereditary breast/ovarian cancer syndrome this includes: women with a personal history of both breast and ovarian cancer; women with ovarian cancer and a close relative with breast cancer at age 50 years or younger or ovarian cancer at any age; women with ovarian cancer at any age who are of Ashkenazi Jewish ancestry; and women with a first- or second-degree relative with a known *BRCA1* or *BRCA2* mutation [24].

The evaluation of the endometrium is important in detecting occult disease: it is recommended that endometrial sampling be performed at the time of fertility-sparing surgery especially in cases of endometrioid histologies. Zaino *et al.* noted as many as 10% of patients with endometrioid ovarian carcinoma also had a secondary carcinoma of the endometrium at the time of surgery [25].

Assisted reproductive technologies (ART) are controversial in the case of epithelial ovarian carcinomas. The majority of patients in Table 3 did not receive ART and, if more patients had, then the pregnancy rate might have been higher. There are many unresolved issues relating to ART and EOC, including timing of ART initiation after fertility-preserving surgery, prognostic implications of ART on EOC, and the proper follow-up methods when ART is used. Some recent studies have shown no association between ART and decreased survival [26].

In summary, all patients with epithelial ovarian carcinoma should undergo comprehensive surgical staging, and fertility-sparing surgery should be limited to patients with stage IA–IC disease who do not have any of the following additional risk factors: grade 3 disease or clear-cell carcinoma. In women with EOC who undergo conservative surgery, postsurgery surveillance is extremely important and special consideration should be made regarding what should be done

at the completion of childbearing, how *BRCA* patients should be counseled, the evaluation of the endometrium and the use of ART.

Chemotherapy effects on female fertility

One should consider any cytotoxic effects on ovarian tissue when adjuvant chemotherapy is administered to improve the survival of patients undergoing fertility-preserving treatment. The cytotoxic effects of contemporary regimens of chemotherapy, largely comprising paclitaxel and carboplatin, have not been elicited. This is in contrast to the past regimens, which involved alkylating agents, including cyclophosphamide, which has frequently been used in the treatment of childhood cancer and is far more gonadotoxic than other chemotherapeutic agents. Chemotherapeutic agents differ in relation to their toxicity on ovarian function. Cyclophosphamide is a cell-cycle-nonspecific drug; therefore, it is more cytotoxic to the ovaries than cell-cycle-specific drugs, since it affects both dividing cells and resting cells [27]. Taxanes inhibit the function of the mitotic spindle and appear to have a lower likelihood of causing persistent ovarian dysfunction [28].

In a recent Gynecologic Oncology Group (GOG) study, Gershenson *et al.* investigated the reproductive function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors, in which 87% of fertile survivors were still having menstrual function at the time of the study [29].

In one study of 26 patients with ovarian dysgerminoma treated with platinum-based chemotherapy plus surgery at MD Anderson (TX, USA), 16 patients underwent fertility-sparing surgery and, of these, 71% continued to have normal menstrual function during chemotherapy and after, and 93% returned to their prechemotherapy menstrual pattern years after chemotherapy was over. Out of these 16 patients, five pregnancies have occurred [30].

Among the studies in Table 2, Gershenson reported favorable outcomes after chemotherapy for malignant disease [10]. In the studies reviewed in Table 3, the majority of patients with stage IC disease or greater or with high-risk features, such as moderate- or high-grade histology, received adjuvant chemotherapy. Despite this, the majority of patients in Table 3 who attempted pregnancy succeeded, and although there was a high frequency of patients who received chemotherapy in the Park *et al.* study, there were no congenital anomalies [15].

Fertility preservation options

In addition to fertility-sparing surgery for EOC that includes a unilateral salpingo-oophorectomy and staging, stage IB patients who have bilateral ovarian cancer may undergo BSO with uterine preservation. This fertility-sparing approach allows for ovum donation, which is successful in patients without functioning ovaries. Alternatively, gestational carriers enable women without uteri to produce biologic offspring. Women who undergo conservative, fertility-sparing management of ovarian cancer often delay childbearing to ensure that they will most likely survive their disease. The issue with delaying childbearing introduces the additional risks that age independently places on childbearing, such as increased risk of miscarriage and increased risk of Down syndrome in women over the age of 35 years, and especially over the age of 40 years. In this situation, embryo cryopreservation provides an option for delaying reproduction.

Cryopreservation has emerged as a fertility preservation option and consists of various forms, including embryo, oocyte and ovarian tissue cryopreservation. Embryo cryopreservation is widely available with established success, whereas oocyte and ovarian tissue cryopreservation are investigational. Cryopreservation is extremely important for women with more advanced stages of cancer to preserve fertility potential. In general, the harvesting of eggs in cancer patients is controversial in that some cancers are particularly sensitive to estrogen. The use of ART in women who have a history of ovarian cancer remains controversial yet feasible.

A study carried out by Oktay *et al.* compared ovarian stimulation in patients with breast cancer, an estrogen-sensitive malignancy, with tamoxifen alone, tamoxifen with follicle stimulating hormone (FSH), and letrozole with FSH in order to see which combination would allow more oocytes to be obtained without causing a significant rise in serum estrogen. Patients treated with tamoxifen with FSH, or letrozole with FSH, had greater numbers of follicles, mature oocytes and embryos than those treated with tamoxifen alone; in addition, peak estradiol levels were lower with letrozole and tamoxifen than with tamoxifen and FSH [31]. This suggests that letrozole in combination with FSH may be the preferred method for ovarian stimulation in women with estrogen-sensitive malignancies. Although ovarian cancer is not thought of specifically as an estrogen-sensitive malignancy, research is ongoing regarding possible potentiation of tumor growth. In addition, we do not know the specific

roles of α and β estrogen receptors, which have been seen on tumor cells of the ovary both in *BRCA* carriers and non-*BRCA* carriers. There have been data to suggest a possible link between fertility drugs and patients with synchronous endrometrioid tumors of the endometrium and ovary, which are generally found in younger women than either adenocarcinomas or ovarian adenocarcinomas [32].

In embryo cryopreservation, cancer treatment must be withheld for oocytes to be collected and *in vitro* fertilization to occur. Reported survival rates per thawed embryo range from 35 to 90%, implantation rates from 8 to 30%, and cumulative pregnancy rates up to 60% [31].

While still an experimental technique, oocyte preservation is an attractive option compared with embryo cryopreservation since it does not require a male partner or surgery. However, similar to embryo cryopreservation, this technique does require ovarian stimulation and completion of an *in vitro* fertilization stimulation cycle before cancer therapy can begin, which may not be possible in situations in which chemotherapy must be started immediately. Unfortunately, pregnancy rates following transfer of thawed oocytes have been quite low. Sonmezer and Oktay calculated a mean survival rate of 47% based on 21 studies, a fertilization rate of 52% and a pregnancy rate per thawed oocyte of only 1.52% [33]. These pregnancy rates improve slightly with the use of vitrification and intracytoplasmic sperm injection, but remain significantly lower than that of other ART.

Cryopreservation of primordial follicles within ovarian tissue has potential advantages over both embryo and oocyte freezing. Primordial follicles are less susceptible to cryoinjury than are mature oocytes and may be preserved without a delay in cancer treatment. The principal challenge to the success of this technique is ischemic damage, which occurs after thawing and transferring either orthotopically or heterotopically owing to the lack of adequate blood supply [34,35]. For this reason, it seems that excising the whole ovary with its vascular pedicle for later reanastamosis is preferable to the cryopreservation of ovarian cortical strips [34,35]. This technique is also more surgically invasive than other methods.

Another concern is the potential for reseeding tumor cells following ovarian transplantation in cancer patients. In order to minimize this risk, histologic evaluation should always be performed on multiple harvested ovarian tissue samples [36]. Oktay *et al.*, in 2001, were the first to report the return of ovarian endocrine function following heterotopic transplantation of cryopreserved ovarian tissue [37]. More recently, Oktay *et al.* were able to restore ovarian function by transplanting cryopreserved ovarian tissue beneath the abdominal skin [38]. They were able to produce a four-cell embryo that was transferred to the patient, but pregnancy did not occur [38]. Despite these challenges, a recent report by Donnez *et al.* describes the first pregnancy occurring after orthotopic transplantation of cryopreserved ovarian tissue and imparts encouragement to the field [39]. However, this study has been criticized as failing to provide definitive evidence that the pregnancy resulted from cryopreserved and transplanted ovarian tissue as the patient had not undergone oophorectomy [40].

Meirow *et al.* report a case of a live birth after *in vitro* fertilization following the transplant of thawed cryopreserved ovarian cortical tissue into the ovaries of a 28-year-old woman who had ovarian failure after high-dose chemotherapy for non-Hodgkin's lymphoma [41]. Transplantation of thawed cryopreserved ovarian tissue occurred after 24 months of persistent ovarian failure [41]. Strips of thawed ovarian tissue were transplanted to one ovary and small fragments were injected into the other [41]. A total of 8 months after transplant, the patient spontaneously menstruated [41]; 9 months after transplant, after a modified natural cycle, the mature egg was retrieved and fertilized *in vitro* [41]. A four-cell embryo was transferred back to the uterus and the patient subsequently had a normal intrauterine pregnancy [41]. Although the possibility that the egg was derived from the native ovary cannot be ruled out, this is extremely unlikely given the consistent evidence of ovarian failure after high-dose chemotherapy and the timing of restoration of ovarian function after transplantation.

Silber *et al.* describe a case of ovarian transplantation between monozygotic twins in which the recipient had unexplained premature ovarian failure [42]. Large pieces of fresh ovarian cortex were grafted to the recipient's streak ovaries and 3 months after transplant the recipient's cycles resumed [42]. During the second cycle she spontaneously conceived and subsequently her pregnancy progressed uneventfully [42]. Although this case may not be relevant to cancer patients, this and other similar studies illustrate tissue viability following microsurgical techniques [41,42]. These findings suggest that transplantation of cryopreserved ovarian tissue can be successfully performed in humans and may have utility, as technological advances develop, as a potential fertility option for cancer survivors.

There is very limited overall experience with autotransplantation and only a few cases have been reported in the literature. A recent publication from Denmark describes two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue that was removed from women with malignant disease [43]. In this study, one complete ovary was cryopreserved from each of six patients who were aged 26–35 years prior to treatment. Four of the six women conceived following assisted reproduction, although one miscarried, and one had a positive human chorionic gonadotrophin but no clinical pregnancy, and two delivered healthy children. Although only one ovary was removed in each of these six cases, all patients were subsequently given gonadotoxic treatment, and the remaining ovary showed no activity. All six patients experienced resumption of ovarian activity following transplantation. Owing to unknown lifespan and quality of the grafts, all patients were offered assisted reproduction in order to increase the chance of conception.

One recent retrospective study evaluated the use of ovarian cryopreservation specifically in women with borderline ovarian tumors. Specific to women with ovarian cancer, one very important consideration is the ability to get 'healthy' ovarian tissue. In this particular study, the pathologist macroscopically selected a part of the ovary without disease [44]. If there is no healthy part of the ovary larger than 4–5 mm, then ovarian cryopreservation cannot be performed; therefore, cryopreservation is more limited when dealing with ovarian cancer in comparison to using it for other malignancies because the tumor is located in the organ that will subsequently be preserved, and this raises the question of the safety of subsequent reimplantation of the ovarian tissue fragments.

Conclusion

Fertility preservation in young women diagnosed with cancer has become an important aspect of cancer treatment as survival rates continue to improve. Fertility-sparing surgeries for women with early-stage malignancies have proven efficacy in preserving fertility without apparent adverse impact on cancer outcomes. Advances in ART have provided patients with more fertility options.

Two of the key issues in the management of women with gynecologic malignancies who desire fertility preservation are thorough patient counseling by both gynecologic oncologists and fertility specialists, and accurate diagnosis. Preoperative counseling requires the combined collaborative efforts of gynecologic oncologists and reproductive endocrinologists. Many of these techniques and treatment strategies have only been studied in small series and are not considered standard of care. Women considering nontraditional therapy need to understand the inherent risks of residual microscopic disease, failed therapy and cancer recurrence when selecting for fertility preservation. This inherent risk of adverse outcomes with fertility preservation, despite in many instances the small body of literature to the contrary, must be communicated to and acknowledged by the patient. Some women may die secondary to recurrent malignancies when these methods are employed; thus, patient selection and counseling are cornerstones of care. In addition, the limitations of ART should be detailed so that women and their partners have realistic expectations of the likelihood of producing biologic offspring. Furthermore, women must be willing to accept the unidentified risks due to our lack of knowledge of long-term consequences of ART in the setting of ovarian cancer.

A requisite of successful conservative management is an accurate diagnosis. This may require further analysis and a need for reoperation. For example, a candidate with positive lymph nodes or evidence of abdominal spread is not a candidate for conservative therapy. Thus, a revised treatment plan may be made intra- or post-operatively. Each case requires unique consideration by subspecialists to avoid potentially fatal management errors.

Furthermore, the association between ovulation-inducing agents and some cancers is unclear [45]. There have been reports of infertile women who underwent assisted reproduction and were subsequently diagnosed with ovarian cancer [46,47]. The association between fertility drugs and ovarian cancer is complicated by the fact that infertility increases ovarian cancer risk. Clinical studies that have suggested a link are difficult to interpret given the small numbers, short follow-up and inability to control for other cancer predictors, and they have not been replicated by more recent investigations [45].

Future perspective

Further clinical trials are needed to establish prognostic equivalence for many of the aforementioned strategies; nonetheless, with proper patient selection and careful counseling, a number of these techniques can be offered to patients who desire to preserve fertility. Further research is also needed on oocyte and ovarian tissue

cryopreservation; however, recent data involving these techniques highlight the vast potential to effectively preserve fertility in cancer survivors.

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Executive summary

Low malignant potential tumors

- Many conservative options are available. Although recurrence is higher, they have excellent long-term survival rates.
- After conservative surgery, approximately half of patients attempting to conceive become pregnant.
- Conservative therapy is an acceptable option for women wishing to conserve fertility.

Germ cell malignancies

- Conservative surgery with chemotherapy is an acceptable option to preserve fertility, even at advanced stages.
- Up to 80% of patients attempting to conceive after conservative therapy become pregnant.

Epithelial ovarian carcinoma

- Low malignant potential tumors have an excellent 5-year survival rate, despite being more aggressive, and are being diagnosed earlier; thus, a focus on fertility preservation is increasing.
- Although recurrences are greater for epithelial ovarian carcinomas past stage IA, survival rates after conservative surgery are comparable to radical surgery up to stage IC.
- Among patients attempting to conceive, over 75% became pregnant after conservative surgery.
- For staging considerations, laparoscopic fertility-sparing surgery improves postoperative outcomes, the endometrium should be inspected at the time of staging, and special considerations should be made for *BRCA1/2* patients.

Chemotherapy effects on female fertility

- Newer forms of chemotherapy, such as taxanes and platinum derivatives, are less toxic to the ovary.
- Chemotherapy is associated with positive pregnancy outcomes.

Fertility preservation options

- Cryopreservation is an emerging option for fertility preservation, although its use is controversial as it may potentiate estrogen-sensitive tumors.
- Oocyte cryopreservation has some advantages over embryo cryopreservation, but pregnancy rates are lower.
- Many case reports describe successful pregnancies after cryopreservation and transplantation.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Jemal A, Siegel R, Ward E *et al.*: Cancer statistics, 2008. *CA Cancer J. Clin.* 58, 71–96 (2008).

2 Kosary CL: Cancer of the ovary. In: *SEER Cancer Statistics Review, 1975–2006.* Horner MJ, Ries LAG, Krapcho M *et al.* (Eds). National Cancer Institute, MD, USA (2009).

3 Wenzel L, Dogan-Ates A, Habbal R *et al.*: Defining and measuring reproductive concerns of female cancer survivors. *J. Natl Cancer Inst. Monogr.* (34), 94–98 (2005).

4 Borgfeldt C, Iosif C, Masback A: Fertility-sparing surgery and outcome in fertile women with ovarian borderline tumors and epithelial invasive ovarian cancer. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 134, 110–114 (2007).

▪ **Swedish study evaluating fertility sparing surgery in borderline and epithelial ovarian tumors.**

5 Gotlieb WH, Flikker S, Davidson B *et al.*: Borderline tumors of the ovary. *Cancer* 82, 141–146 (1998).

▪ **Retrospective review of borderline tumors of the ovary in Israel.**

6 De Iaco P, Ferrero A, Rosati F *et al.*: Behavior of ovarian tumors of low malignant potential treated with conservative surgery. *Eur. J. Surg. Oncol.* 35, 643–648 (2009).

7 Tinelli R, Tinelli A, Tinelli FG, Cicinelli E, Malvasi A: Conservative surgery for borderline ovarian tumors: a review. *Gynecol. Oncol.* 100(1), 185–191 (2006).

▪ **Review of fertility sparing surgery in borderline ovarian tumors.**

8 Fauvet R, Poncelet C, Boccara J, Descamps P, Fondrinier E, Daraï E: Fertility after conservative treatment for borderline ovarian tumors: a French multicenter study. *Fertil. Steril.* 83(2), 284–290 (2005).

▪ **French multicenter study of fertility after conservative treatment for borderline ovarian tumors.**

9 Peccatori F, Bonazzi C, Chiari S *et al.*: Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. *Obstet. Gynecol.* 86, 367–372 (1995).

10 Gershenson D: Management of ovarian germ cell tumors. *J. Clin. Oncol.* 25(20), 2938–2943 (2007).

▪▪ **Review of the management of ovarian germ cell tumors.**

11 Nishio S, Ushijima K, Fukui A *et al.*: Fertility-preserving treatment for patients with malignant germ cell tumors of the ovary. *J. Obstet. Gynaecol.* 32(4), 416–421 (2006).

▪▪ **Review of fertility sparing surgery in malignant germ cell tumors of the ovary.**

12 Tangir J, Zelterman D, Ma W, Schwartz PE: Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. *Obstet. Gynecol.* 101(2), 251–257 (2003).

13 Gershenson DM: Fertility-sparing surgery for malignancies in women. *J. Natl Cancer Inst. Monogr.* 34, 43–47 (2005).

14 Morice P, Leblanc E, Rey A *et al.*; GCCLCC and SFOG: Conservative treatment in epithelial ovarian cancer: results of a multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer) and SFOG (Societe Francaise d'Oncologie Gynecologique). *Hum. Reprod.* 20, 1379–1385 (2005).

15 Park J, Kim D, Suh D *et al.*: Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: oncologic safety and reproductive outcomes. *Gynecol. Oncol.* 110, 345–353 (2008).

▪▪ **Evaluation of the safety and reproductive outcome in fertility-sparing surgery for invasive epithelial ovarian cancer.**

16 Munnell EW: Is conservative therapy ever justified in stage I(IA) cancer of the ovary? *Am. J. Obstet. Gynecol.* 103, 641–653 (1969).

▪ **Discussion of conservative therapy for stage IA cancer of the ovary.**

17 Benjamin I, Morgan MA, Rubin SC: Occult bilateral involvement in stage I epithelial ovarian cancer. *Gynecol. Oncol.* 72, 288–291 (1999).

18 Zanetta G, Chiari S, Rota S *et al.*: Conservative surgery for stage I ovarian carcinoma in women of childbearing age. *Br. J. Obstet. Gynaecol.* 104, 1030–1035 (1997).

▪ **Review of fertility sparing surgery in stage I ovarian cancer.**

19 Anchezar J, Sardi J, Soderini A: Long-term follow-up results of fertility-sparing surgery in patients with epithelial ovarian cancer. *J. Surg. Oncol.* 100, 55–58 (2009).

▪ **Retrospective review of fertility-sparing surgery in patients with epithelial ovarian cancer.**

20 Angioli R, Muzii L, Battista C *et al.*: The role of laparoscopy in ovarian carcinoma. *Minerva Ginecol.* 61(1), 35–43 (2009).

21 Chi DS, Abu-Rustum NR, Sonoda Y *et al.*: The safety and efficacy of laparoscopic surfical staging of apparent stage I ovarian and fallopian tube cancers. *Am. J. Obstet. Gynecol.* 192(5), 1614–1619 (2005).

22 Ghezzi F, Cromi A, Siesto G *et al.*: Use of laparoscopy in older women undergoing gynecologic procedures: is it time to overcome initial concerns? *Menopause* 17(1), 96–103 (2010).

23 Schmeler KM, *et al.*: Prophylactic bilateral salpingo-oophorectomy compared with surviellance in women with BRCA mutations. *Obstet. Gynecol.* 108(3), 515–520 (2006).

24 Lancaster JM, Powell CB, Kauff ND *et al.*: Society of Gynecologic Oncologists education committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol. Oncol.* 107, 159–162 (2007).

25 Zaino R, Whitney C, Brady MF *et al.*: Simultaneously detected endometrial and ovarian carcinomas – a prospective clinicopathologic study of 74 cases. A Gynecologic Oncology Group study. *Gynecol. Oncol.* 83, 355–362 (2001).

26 Douglas NC, Fan L, Pothuri B, Herzog TJ, Sauer MV: Fertility sparing therapy for ovarian cancer has inherent risks and benefits. *Arch. Gynecol. Obstet.* 272, 304–308 (2005).

27 Schmidt KT, Larsen EC, Andersen CY, Andersen AN: Risk of ovarian failure and fertility preserving methods in girls and adolescents with a malignant disease. *BJOG* 117, 163–174 (2010).

28 Gadducci A, Cosio S, Genazzani AR: Ovarian function and childbearing issues in breast cancer survivors. *Gynecol. Endocrinol.* 23(11), 625–631 (2007).

29 Gershenson DM, Miller AM, Champion VL *et al.*: Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group study. *J. Clin. Oncol.* 25(19), 2792–2797 (2007).

30 Brewer M, Gershenson DM, Herzog CE *et al.*: Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. *J. Clin. Oncol.* 17, 2670–2675 (1999).

31 Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z: Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J. Clin. Oncol.* 23(19), 4347–4353 (2005).

32 Grammatoglou X, Skafida E, Glava C *et al.*: Synchronous endometrioid carcinoma of the uterine corpus and ovary. A case report and review of the literature. *Eur. J. Gynaecol. Oncol.* 30(4), 437–439 (2009).

33 Sonmezer M, Oktay K: Fertility preservation in female patients. *Hum. Reprod. Update* 10, 251–266 (2004).

34 Bedaiwy MA, Falcone T: Ovarian tissue banking for cancer patients: reduction of post-transplantation ischemic injury: intact ovary freezing and transplantation. *Hum. Reprod.* 19, 1242–1244 (2004).

35 Martinez-Madrid B, Dolmans MN, van Langendonckt A *et al.*: Freeze–thawing intact human ovary with its vascular pedicle with a passive cooling device. *Fertil. Steril.* 82, 1390–1394 (2004).

36 Revel A, Schenker J: Ovarian tissue banking for cancer patients: is ovarian cortex cryopreservation presently justified? *Hum. Reprod.* 19, 14–19 (2004).

37 Oktay K, Economos K, Kan M *et al.*: Endocrine function and oocyte retrieval after autologus transplantation of ovarian cortical strips to the forearm. *JAMA* 286, 1490–1493 (2001).

▪ **Case review of autologous transplantation of ovarian cortical strips into the forearm and oocyte retrieval.**

38 Oktay K, Buyuk E, Veeck L *et al.*: Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. *Lancet* 363, 837–840 (2004).

39 Donnez J, Dolmans MM, Demylle D *et al.*: Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* 364, 1405–1410 (2004).

40 Oktay K, Tilly J: Livebirth after cryopreserved ovarian tissue autotransplantation. *Lancet* 364, 2091–2092 (2004).

41 Meirow D, Levron J, Eldar-Geva T *et al.*: Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. *N. Engl. J. Med.* 353, 318–321 (2005).

42 Silber SJ, Lenahan KM, Levine DJ *et al.*: Ovarian transplantation between monozygotic twins discordant for premature ovarian failure. *N. Engl. J. Med.* 353, 58–63 (2005).

43 Andersen CY, Rosendahl M, Byskov AG *et al.*: Two successful pregnancies following autotrasplantation of frozen/thawed ovarian tissue. *Hum. Reprod.* 23(10), 2266–2272 (2008).

44 Fain-Kahn V, Poirot C, Uzan C *et al.*: Feasibility of ovarian cryopreservation in borderline ovarian tumours. *Hum. Reprod.* 24(4), 850–855 (2009).

45 Lobo RA: Potential options for preservation of fertility on women. *N. Engl. J. Med.* 353, 64–73 (2005).

46 Brinton LA, Moghissi KS, Scoccia B, Westhoff CL, Lamb EJ: Ovulation induction and cancer risk. *Fertil. Steril.* 83, 261–274 (2005).

47 Makrydimas G, Sotiriadis A, Paraskevaidis E, Pavlidis N, Agnantis N, Lolis D: Clear cell ovarian carcinoma in a pregnant woman with a history of infertility, endometriosis and unsuccessful IVF treatment. *Eur. J. Gynaecol. Oncol.* 24, 438–441 (2003).

48 Morris RT, Gershenson DM, Silva EG, Follen M, Morris M, Wharton JT: Outcome and reproductive function after conservative surgery for borderling ovarian tumors. *Obstet. Gynecol.* 95(4), 541–547 (2000).

49 Zanetta G, Rota S, Chiari S *et al.*: Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. *J. Clin. Oncol.* 19, 2658–2664 (2001).

50 Morice P, Camatte S, El Hassan J, Pautier P, Duvillard P, Castaigne D: Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors. *Fertil. Steril.* 75, 92–96 (2001).

51 Camatte S, Morice P, Pautier P, Atallah D, Duvillard P, Castaigne D: Fertility results after conservative treatment of advanced stage serous borderline tumour of the ovary. *BJOG* 109(4), 376–380 (2002).

52 Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH: Surgical management of borderline ovarian tumors: the role of fertility-sparing surgery. *Gynecol. Oncol.* 113, 75–82 (2009).

53 Uzan C, Kane A, Rey A, Gouy S, Duvillard P, Morice P: Outcomes after conservative treatment of advanced-stage serous borderline tumors of the ovary. *Ann. Oncol.* 21, 55–80 (2009).

54 Low J, Perrin L, Cradnon A, Hacker N: Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. *Cancer* 89(2), 391–398 (2000).

55 Zanetta G, Bonazzi C, Cantú M *et al.*: Survival and reproductive function after treatment of malignant germ cell ovarian tumors. *J. Clin. Oncol.* 19(4), 1015–1020 (2001).

56 Zanagnolo V, Sartori E, Galleri G, Pasinetti B, Bianchi U: Clinical review of 55 cases of malignant ovarian germ cell tumors. *Eur. J. Gynaecol. Oncol.* 25(3), 315–320 (2004).

57 Chan J, Tewari K, Waller S *et al.*: The influence of conservative surgical practices for malignant ovarian germ cell tumors. *J. Surg. Oncol.* 98(2), 111–116 (2008).

58 Morice P, Wicart-Poque F, Rey A *et al.*: Results of conservative treatment in epithelial ovarian carcinoma. *Cancer* 92, 2412–2418 (2001).

59 Schilder J, Thompson M, DePriest AP *et al.*: Outcome of reproductive-age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. *Gynecol. Oncol.* 87, 1–7 (2002).

60 Schlaerth A, Chi D, Poynor E, Barakat R, Brown C: Long-term survival after fertility-sparing surgery for epithelial ovarian cancer. *Int. J. Gynecol. Cancer* 19, 1199–1204 (2009).

61 Raspagliesi F, Fontanelli R, Palladini D *et al.*: Conservative surgery in high-risk epithelial ovarian carcinoma. *J. Am. Col. Surg.* 185, 457–460 (1997).

62 Kwon Y, Hahn H, Kim T *et al.*: Fertility preservation in patients with early epitheial ovarian cancer. *J. Gynecol. Oncol.* 20, 44–47 (2009).