



Ovarian preservation in gynecologic oncology: current indications and techniques

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Purpose of review

Early menopause represents a relevant clinical issue for women. Nevertheless, this issue should be balanced with the risks of ovarian metastasis, ovarian recurrence, and the risk of recurrence in hormone-sensitive gynecological cancers. The purpose of this review was to provide an overview on current indications and techniques of ovarian preservation in patients with gynecological cancers.

Recent findings

The potential discussion about ovarian conservation could be proposed to patients with FIGO-stage IA grade 1-2 endometrioid endometrial cancer aged 40 years or less, FIGO-stage IB1-IB2 node-negative cervical cancer with squamous cell carcinoma and HPV-associated adenocarcinoma, FIGO-stage IA-IC grade 1-2 serous, endometrioid, mucinous expansile pattern ovarian cancer, any stage germ cell ovarian tumors, and FIGO-stage IA sex cord-stromal tumors. Technique to perform ovarian transposition in cervix cancer is also reported.

Summary

Ovarian conservation is a surgical approach that involves preserving one or both ovaries during the treatment of gynecologic cancers. This approach has gained popularity in recent years, as it offers several benefits to the patient, including the preservation of hormonal function and fertility. The decision to perform ovarian conservation depends on several factors, such as the stage and type of cancer, the patient's age, fertility desire, and should be carefully discussed with patients.

Keywords

gynecological cancer, menopause, ovarian conservation, recurrence, survival

INTRODUCTION

It is estimated that 4570 women died of cancer in the age between 20 and 39 years in the United States in 2019 [1]. In this context, gynecological malignancies might be diagnosed in patients in premenopausal age [2]. Endometrial cancer occurs in 15% of cases in premenopausal women and just over 1% of patients are diagnosed before 40 years of age [3]. Cervical cancer represents the second cause of cancer death in patients in women aged 20–39 years and half of cervix cancer diagnoses are made in patients younger than 50-year-old [1]. Ovarian preservation can be considered both in the early-stage and in the locally advanced stage settings, thanks to the technique of ovarian transposition, indicated in both situations [4,5].

Vulvar and vaginal cancers are rare gynecological malignancies primarily affecting postmenopausal women. It is estimated that about 20 and 15% of vulvar and vaginal cancers are diagnosed in women younger than 50 years of age, respectively [6,7].

Concerning ovarian cancer, it is reported that 73% of epithelial histotype occur after menopause, while nonepithelial ovarian cancers are more frequent in the premenopausal age [8,9].

The burden of gynecological cancers in young patients represents a challenge for the gynecologic oncologists who have to face the balance between the risk of ovarian metastasis (cancer implants on the ovary at time of diagnosis) or ovarian recurrence

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KEY POINTS

- The decision to perform ovarian conservation in patients with gynecologic cancers depends on several factors, including the stage and type of cancer, the patient's age, and fertility goals.
- Consequences related to surgically induced menopause should be balanced with the risks of ovarian metastasis, ovarian recurrence, and recurrence in hormone-sensitive gynecological cancers.
- Ovarian conservation might be discussed with patients with FIGO-stage IA grade 1-2 endometrioid endometrial cancer aged 40 years or less, FIGO-stage IB1-IB2 node-negative cervical cancer, FIGO-stage IA-IC grade 1-2 serous, endometrioid, mucinous expansile pattern ovarian cancer, any stage germ cell ovarian tumors, and FIGO-stage IA sex cord-stromal tumors.
- Ovarian transposition in patients with cervical cancer undergoing pelvic radiotherapy should always be considered, performed with lateral approach, minimally invasive surgery, and considering extraperitoneal tunneling of infundibulo-pelvic ligament after balancing the risk of ovarian recurrence/metastasis.

(recurrence on the preserved ovary) in case of ovarian conservation and the risk of early menopause associated to bilateral oophorectomy [10,11²²]. Surgically induced menopause represents a relevant clinical issue for women. It is estimated that patients undergoing early menopause have an increased risk of death due to cardiovascular disease or to bone fracture due to osteoporosis [12,13]. Another risk of ovarian preservation is related to the potential increased risk of recurrence in hormone-dependent tumors such as endometrial cancer [14,15]. The decision to perform ovarian conservation depends on several factors, such as the stage and type of cancer, the patient's age, and their fertility goals.

With the present review of the literature, we aim to provide an overview on current indications and techniques of ovarian preservation in patients with gynecological cancers focusing on the studies published in the last 2 years. Preinvasive disease and borderline tumors were excluded from the scope of this article.

ENDOMETRIAL CANCER

Endometrial cancer is diagnosed in 2–14% in women 40 years of age and younger. Most of these patients have an identifiable source of excess estrogen, while in a small subset, the pathogenesis is related to mismatch repair abnormality and Lynch syndrome [16,17]. In a study from 2019, Mandelbaum *et al.*

[18] described the patterns of utilization and outcomes of ovarian conservation for young women with minimal-risk endometrial cancer with a population-based retrospective analysis of the Nationwide Inpatient Sample. The authors showed that ovarian conservation rates ranged from 11.7 to 60.5% and concluded that there was substantial variability in the utilization of ovarian conservation in young women with low-risk endometrial cancer based on patient, surgical, and hospital factors [18].

Ovarian recurrence

Two retrospective studies specifically looked at the oncological safety of ovarian preservation in early-stage endometrial adenocarcinoma [19²³,20]. Nasioudis *et al.* [19²³] analyzed 2941 patients aged 45 years or less diagnosed between January 2004 and December 2015 with FIGO-stage I grade 2 or 3 endometrioid endometrial carcinoma, who underwent hysterectomy with or without bilateral salpingo-oophorectomy from the National Cancer Database [19²³]. Two hundred (6.8%) patients did not undergo bilateral salpingo-oophorectomy. Rate of ovarian preservation was comparable between patients with grade 2 (6.6%) and grade 3 (7.7%) tumors. Patients who did not undergo bilateral salpingo-oophorectomy were younger and less likely to undergo surgical lymph node assessment (52 vs. 76.2%). There was no difference in overall survival (OS) between patients who did and did not undergo bilateral salpingo-oophorectomy; 5-year OS was 96.6 and 97%, respectively. After controlling for confounders, including tumor grade, ovarian preservation was not associated with worse OS. The authors concluded that for patients with grade 2-3 FIGO-stage I endometrioid carcinoma undergoing hysterectomy, ovarian preservation is rarely performed while no clear detrimental effect on OS was found. Similar conclusion was reached by Akgour *et al.* In their retrospective study, they analyzed 169 patients with FIGO-stage I grade 1–3 aged 40 years or less, of whom 54 (31.9%) underwent ovarian preservation, while 115 (68.1%) underwent bilateral salpingo-oophorectomy. No difference in recurrence-free and OS was observed between the two groups. The authors concluded that ovarian preservation appears to be well tolerated without having any adverse impact on survival in women aged 40 years or less with FIGO-stage I endometrial cancer [20]. Interestingly, a recent case report described the ovarian recurrence 12 months after primary treatment of a postmenopausal woman with FIGO-stage IA grade 1 endometrioid endometrial adenocarcinoma [21]. In general, there is a relative lack of data available for ovarian

preservation in the postmenopausal group and age remains an important risk factor for ovarian recurrence, particularly more than 45 years [22].

Ovarian metastasis

Risk of ovarian metastasis found at time of oophorectomy for endometrial cancer is reported between 2.0 and 8.1% of patients [23]. Risk factors for ovarian metastases were described to be age more than 45 years, myometrial invasion more than 50%, cervical invasion, pelvic lymph node metastasis, nonendometrioid histology, grade 3, extrauterine disease, and presence of LVSI [23–25] (Table 1). Moreover, recently, Xu *et al.* [26] demonstrated that cytokeratin 19 (CK19) serum levels more than 3.3 ng/ml were independent risk predictors of ovarian metastasis in premenopausal women. For this reason, the authors proposed the incorporation of serum CK19 into the preoperative assessment of endometrial cancer, especially as extension of current standard approach with ovarian preservation counseling.

Comment

Overall, the current evidence on the oncological safety of ovarian preservation in FIGO-stage I endometrial cancer derives from retrospective studies with small number of patients (Supplemental Table 1, <http://links.lww.com/COON/A39>); therefore, it must be taken with caution. We might conclude that this approach should be recommended in FIGO-stage IA grade 1-2 endometrioid histology aged 40 years or less and could be discussed with patients in FIGO-stage IA grade 3 endometrioid histology, FIGO-stage IB grade 1-2, and in patients aged 41–45 years.

CERVICAL CANCER

Cervical cancer is the fourth most common cancer in women. In high resource countries, the peak of incidence is reached at age of 40 [27]. For this reason, the issue about ovary conservation in cervical cancer patients is particularly relevant. One study retrospectively analyzed the trends and characteristics of ovarian conservation at time of hysterectomy in young women with cervical cancer examining the National Inpatient Sample. The authors found that ovarian conservation rates remained stable until age of 37 years, ranging from 82.5 to 77.9% of cases, after which time the rate sharply and significantly decreased by 7.4%. Authors concluded that increasing rates of ovarian conservation at the time of hysterectomy in women undergoing surgical management of cervical cancer is encouraging; however,

the marked decrease noted in patients in their mid-30s as well as substantial variability in ovarian conservation based on patient, surgical, and hospital factors are striking and warrant further consideration [28].

Ovarian conservation in cervical cancer is strictly related to the technique of ovarian transposition due to the risk of adjuvant (chemo)radiotherapy after radical surgery (estimated between 17 and 49% of cases [29,30]) or to the treatment of locally advanced stage with exclusive chemo-radiotherapy [31]. In this context, it is known that a radiotherapy dose of 10 Gy can be sufficient to cause a premature ovarian failure [32].

Ovarian recurrence

A recent meta-analysis investigated the outcomes of ovarian transposition who underwent surgery with or without adjuvant radiotherapy [33]. The risk of ovarian recurrence and of ovarian cyst formation on the conserved ovaries was found in 4 of 1160 (0.3%) and in 125 of 1160 (10.8%) patients. Moreover, ovarian function was retained in more than two-thirds of patients (70.6%). Similar results in terms of risk of ovarian recurrence were reported by a retrospective multicenter study comparing the outcomes of patient undergoing and not undergoing ovarian conservation at time of radical surgery for early-stage cervical cancer [34]. In this study, the authors reported a risk of ovarian recurrence in 2 of 155 (1.3%) patients and they highlight the potential underestimation of the incidence of ovarian recurrence that could be misdiagnosed with a peritoneal metastasis (in transposed ovaries) or a lymph node recurrence (in nontransposed ovaries) if not surgically explored. Interestingly, in this study, patients undergoing ovarian conservation had a better disease-free survival (DFS) (and a trend toward a better OS) compared with those who underwent oophorectomy at time of radical surgery. The authors discuss about the potential protective role of estrogen and progesterone toward cervical carcinoma recurrence, as reported by previous studies [35,36].

Another retrospective study focused on the oncological outcomes of patients with adenocarcinoma or adenosquamous histology only who underwent ovarian conservation vs. oophorectomy at time of radical surgery [37]. The authors did not find a difference in recurrence-free and OS in the two study groups. Moreover, there was no evidence of ovarian recurrence or metachronous ovarian cancer in patients who underwent ovarian conservation (Table 1).

Despite older than 2 years, a retrospective study analyzing the oncologic outcomes of 9419 patients

Table 1. Studies analyzing the outcomes of patients undergoing ovarian conservation in early-stage cervical cancer

YEAR	AUTHOR/ JOURNAL	STUDY DESIGN	AIM	SAMPLE SIZE	AGE (median)		FUP (MONTHS)		5-year RFS		5-year OS		RECUR- RENCE		OVARIAN		CONCLUSION
					OVP	OOPH	OVP	OOPH	OVP	OOPH	OVP	OOPH	OVP	OOPH	OVP	OOPH	
2021	Theplib <i>et al.</i> [37]	retrospective	incidence of ovarian metastasis and the impact of ovarian preservation on oncological outcomes	196	3	38	45	72	88.90%	91.10%	97.50%	96.50%	14	9	0	0	No incidence of ovarian metastasis, synchronous or metachronous ovarian cancer, or ovarian recurrence was reported in our study, from which we conclude that ovarian preservation may be well tolerated in patients with adenocarcinoma and adenosquamous cervical cancer stages IA2-B1. However, the impact of ovarian preservation on oncological outcomes needs to be further investigated.
2021	Bizzarri <i>et al.</i> [34 ^a]	retrospective	incidence of ovarian metastasis/recurrence and the survival of patients undergoing radical hysterectomy with OVP vs. oophorectomy	419	3	36	44	48	90.60%	82.20%	94.30%	90.80%	14	27	2	1 (0.4%)	OVP was associated with reduced risk of recurrence and menopausal symptoms in early-stage cervical cancer. As the risk of ovarian metastasis and ovarian recurrence is relatively low, OVP in premenopausal women has to be considered

OOPH, oophorectomy; OVP, ovarian preservation.

younger than 50 years with stage I cervical cancer undergoing hysterectomy showed that among young women with stage IA, ovarian conservation at hysterectomy was associated with decreased all-cause mortality including death resulting from cardiovascular disease and other chronic diseases (no cancer-specific survival difference), while in patients with stage IB, both cervical cancer specific survival and OS were similar between ovarian conservation and oophorectomy groups [38].

To the best of our knowledge, no study on the risk of ovarian recurrence in locally advanced cervical cancer patients undergoing ovarian transposition treated with exclusive chemoradiotherapy and brachytherapy was found.

Ovarian metastasis

The risk of ovarian metastasis found at the time of oophorectomy during primary surgical treatment of cervical cancer has been investigated by different studies. One of these reported a risk of ovarian metastasis in one of 264 (0.4%) patients undergoing oophorectomy before 50 years of age [34^{*}]. This single case was represented by endocervical adenocarcinoma. The same study reported a literature review of the studies reporting the incidence of ovarian metastasis from apparent early-stage cervical cancer showing a higher risk for patients with adenocarcinoma (3.4%) compared with those with squamous-cell carcinoma (0.7%). For this reason, another study concentrated on patients with adenocarcinoma and adenosquamous carcinoma and found that out of 173 patients undergoing oophorectomy, no patients had ovarian metastasis from cervical malignancy at disease assessment [37] (Table 1).

Matsuo *et al.* [39] in a study from 2017 examined the incidence of and risk factors for metachronous ovarian cancer among young women with stage I cervical cancer who had ovarian conservation at the time of hysterectomy and found ovarian cancer in 13/4365 (0.3%) of cases. Older age, nonwhite ethnicity, adenocarcinoma or adenosquamous histology, and adjuvant radiotherapy were factors potentially associated with an increased metachronous ovarian cancer risk [39].

Lastly, Matsuo *et al.* [40] published a study with the aim to identify a candidate population for ovarian conservation in young women with clinical stage IB-IIB cervical cancer. In this study including a cohort of 3165 patients younger than 50 years who had oophorectomy at radical hysterectomy, the incidence of ovarian metastasis was 1.0% and concluded that nearly two-thirds of women with clinical stage IB-IIB cervical cancer had no risk factor for

ovarian metastasis or had adenocarcinoma alone; these subgroups had ovarian metastasis rates of around 0.1% and may be a candidate population for ovarian conservation at surgical treatment. The authors identified adenocarcinoma histology, parametrial involvement, uterine corpus tumor involvement, and pelvic/para-aortic nodal metastases as independent risk factors for ovarian metastasis [40].

Comment

Overall, the risk of ovarian recurrence and metastasis in conserved ovary is strictly related to the stage of disease at diagnosis and the presence of unfavorable risk factors. In early-stage disease (tumors <4 cm confined to the cervix, with no evidence of lymph node metastasis), ovarian conservation should be considered in all patients with squamous cell carcinoma and HPV-associated adenocarcinoma in premenopausal age, as promoted by international guidelines [31]. In patients at risk of postoperative adjuvant radiotherapy, ovarian transposition should be considered [41].

Techniques for ovarian transposition in cervical cancer

The harmful effect of radiation therapy on ovarian function is well known [32]. Half of the total number of follicles are destroyed at doses of 2 Gy. Therefore, after pelvic irradiation, ovarian failure rates are close to 100% [42].

Two surgical techniques have been described in the literature: the medial and the lateral approach. However, a review comparing medial and lateral transposition in patients affected by Hodgkin disease showed better outcomes in the lateral technique [43].

In the lateral technique, after a proper vascular pedicle mobilization, ovaries are transposed laterally, with various locations described in literature [44,45]. Higher successful preservation rates are associated with transposition at more than 1.5 cm above the iliac crest and 4 cm outside the radiation field [46–48]. A possible reason for ovarian preservation failure is the migration of the ovaries back into the radiation field due to a loss of tension of the fixation point [49].

Another important technical aspect is the integrity of the vascular pedicle, which could be easily damaged from excessive tension, torsion, or kinking as a result of excessive mobilization or improper manipulation [42].

In early reports, ovarian transposition was performed with an open approach [50,51]. Nowadays, transposition as an independent procedure is

performed via minimally invasive, mainly laparoscopic, approach [52–54]. The retroperitoneal tunneling of the ovarian pedicle is a feasible and safe technique, which allows to reduce the radiation dose to the ovarian vessels and improves the stability of the vascular pedicle, reducing risks of kinking and torsion after surgery [52].

Surgery should start with a clear visualization of the ureteral course, followed by a division of the uterine-ovarian ligament and the meso-ovarium. Ovarian pedicle should be carefully prepared to mobilize and suspend the ovary outside the radiation field, as cranial as possible. Nonadsorbable sutures or surgical clips should be applied to transpose the ovary [41]. Salpingectomy could also be associated at time of ovary transposition as a risk reducing surgery.

Complications after ovarian transposition are rare and mainly related to the development of symptomatic ovarian cysts in 95% of cases [55].

VULVAR AND VAGINAL CANCER

Most of vulvar and vaginal cancers are diagnosed in the postmenopausal age, with an estimate of about 20 and 15% of vulvar and vaginal cancers being diagnosed in women younger than 50 years, respectively [6,7], with an increase of number of cases over time [56]. There are very few reports in literature describing the fertility and the pregnancy outcomes in patients with early-stage [57] or with locally advanced vulvar cancer after radiation therapy [58,59].

OVARIAN CANCER

About 17% of ovarian cancers are diagnosed in women younger than 50 years [60]. It is important to note that the incidence of ovarian cancer varies based on several factors, including age, family history, and genetic mutations. Women with a family history of ovarian cancer or certain genetic mutations, such as BRCA1 and BRCA2 mutations, have a higher risk of developing ovarian cancer and an earlier onset [61].

Although majority of patients with ovarian cancer undergo radical surgery, patients with early-stage disease or a nonepithelial tumor could be offered fertility-sparing surgery. According with the ESGO-ESMO (European Society of Gynecological Oncology – European Society for Medical Oncology) and NCCN (The National Comprehensive Cancer Network) guidelines, unilateral-salpingo-oophorectomy is a viable and well tolerated option for women with conceptional desire in FIGO-stage IA/IC1 low grade serous, grade 1-2 endometrioid

grade, and expansile mucinous tumors [62,63]. Table 2 summarizes the most recent articles looking at ovarian conservation in ovarian cancer.

Extra-ovarian disease

Ovarian preservation does not appear to be a well tolerated option for women with epithelial ovarian cancer that has spread beyond the ovaries due to the high risk of recurrence [64]. However, there have been some cases reported in the literature, which were analyzed in a review by Petrillo *et al.* [65]. The authors identified 21 patients with stage II-III disease who underwent unilateral ovarian preservation. Of these patients, nine (42.8%) experienced recurrence, and five (23.8%) ultimately died. Therefore, radical surgery remains the recommended treatment for advanced epithelial ovarian cancer.

Ovarian cystectomy

Unilateral salpingo-oophorectomy is the mainstay of fertility preserving surgery in invasive ovarian cancer. There is a paucity of data on the clinical outcomes of women undergoing cystectomy as a fertility-preserving option. A recent retrospective study conducted by Kajiyama *et al.* [66] analyzed the outcomes of eight patients with early-stage epithelial ovarian cancer who underwent cystectomy as part of conservative surgery. The results were not entirely favorable with two (25.0%) patients experiencing a recurrence and one (12.5%) who died of disease. For these reasons, the option of cystectomy in early-stage ovarian cancer cannot be recommended with current available evidence.

Epithelial ovarian cancer

Ovarian preservation is considered well tolerated and comparable in terms of oncological outcome patients with early-stage epithelial ovarian cancer with no risk factors (high grade, advanced stage, clear cell histology, or mucinous tumor with infiltrative pattern) [67].

To evaluate the safety after surgery without hysterectomy and/or bilateral salpingo-oophorectomy vs. radical surgery in epithelial ovarian cancer, Xie *et al.* [68^{***}] performed a propensity score matching study identifying patients in the Surveillance, Epidemiology and End Results (SEER) database. Six hundred twenty-five pairs of patients with stage I epithelial ovarian cancer were included. Fertility-sparing surgery (FSS) did not have inferior OS compared with radical surgery both in overall cohort and in matched cohort [68^{***}].

Table 2. Studies analyzing the outcomes of patients undergoing ovarian preservation vs. radical surgery for ovarian cancer

YEAR	AUTHOR/JOURNAL	STUDY DESIGN	SAMPLE SIZE	HYSTIOYPE	GRADE	FSS	AGE			STAGE						
							RADICAL	OVERALL	I	Ia	Ib	Ic	II	IIa	IIb	IIc
2021	Zamani et al. [77]	retrospective	72	Germ cell	NA	23	NA	NA	11	NA	NA	23	NA	NA	NA	38
2022	Swift et al. [71]	retrospective	31	Endometrioid	1	32	42	NA	31	0	0	0	0	0	0	0
2022	Xie et al. [68***]	retrospective	3556	Epithelial	NA	NA	NA	18-50	3556	0	0	0	0	0	0	0
2022	Nasioudis et al. [69]	retrospective	235	Epithelial	NA	NA	NA	18-45	235	0	0	0	0	0	0	0
2022	Nasioudis et al. [69]	review	151	Epithelial	NA	NA	NA	NA	151	0	0	0	0	0	0	0
2022	Wang et al. [81]	retrospective	35	Juvenile granulosa	NA	17	NA	NA	35	0	0	0	0	0	0	0
2022	Prodromidou et al. [73]	review	60	Clear cells	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	Birge et al. [70]	retrospective	66	Epithelial	1-3	32	54	NA	66	43	1	22	0	0	0	0
2022	Lin et al. [72]	retrospective	159	Mucinous	1-3	24	45	31	159	55	0	104	0	0	0	0
2022	Sun et al. [78]	retrospective	240	Sex cord stromal	NA	NA	NA	5-49	240	189	1	50	0	0	0	0
2023	Li et al. [80]	retrospective	107	Sex cord stromal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

YEAR	AUTHOR/JOURNAL	APPROACH	SURGERY			ADJ CHT			DEATHS			5-year DFS			5-year OS			RECURRENCE			OBSTETRICS OUTCOMES		
			FSS	RADICAL	FUP	FSS	RADICAL	FUP	FSS	RADICAL	FSS	RADICAL	FSS	RADICAL	FSS	RADICAL	FSS	RADICAL	FSS	RADICAL	PREGNANCY ATTEMPT	CONCEIVED	BIRTHS
2021	Zamani et al. [77]	NA	NA	NA	60	NA	NA	56	NA	NA	NA	87%	NA	NA	94%	NA	NA	NA	NA	26	NA	NA	19
2022	Swift et al. [71]	NA	11	20	NA	NA	72	NA	NA	NA	NA	90%	84%	100%	92%	1	3	NA	NA	7	5	1	1
2022	Xie et al. [68***]	NA	625	2931	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	Nasioudis et al. [69]	NA	105	130	NA	NA	NA	NA	NA	NA	NA	NA	NA	90%	85%	NA	NA	NA	NA	NA	NA	NA	NA
2022	Nasioudis et al. [69]	NA	151	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	19%	NA	NA	NA	NA	NA	NA	NA	NA
2022	Wang et al. [81]	Laparoscopic	35	NA	31	na	51	6	NA	74.8%	NA	84.4%	NA	84.4%	22%	NA	22%	NA	NA	6	6	6	12
2022	Prodromidou et al. [73]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	89.30%	16.6%	15%	4.5%	4	4	4	3	
2022	Birge et al. [70]	NA	NA	7	38	93.9	1	NA	NA	NA	NA	82.5%	94%	99%	12	6	23	21	24	24	24	24	
2022	Lin et al. [72]	Mixed	78	81	44	56	69	1	1	8	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2022	Sun et al. [78]	NA	124	116	NA	NA	121	8	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2023	Li et al. [80]	NA	54	53	NA	NA	50	2	NA	NA	NA	NA	NA	NA	18%	NA	14	11	8	8	8	8	

FSS, fertility-sparing surgery.

The same conclusion can be made for patients with stage IC2/IC3 epithelial ovarian carcinoma. In this context, Nasioudis *et al.* [69] retrospectively collected 235 cases, of whom 105 (44.7%) underwent conservative surgery. FSS was not associated with worse OS also after controlling for grade and performance of lymphadenectomy. In the same study, the authors performed a systematic review and identified 151 patients with stage IC2/IC3 disease who underwent unilateral ovarian and uterine-sparing surgery with the evidence of 19.3% relapse rate and 6.7% of deaths. Recurrence involved exclusively the ovary in 42% of patients. The authors concluded that in a large cohort of patients with stage IC2/IC3 epithelial ovarian carcinoma, FSS was not associated with worse OS, although the relapse rate was approximately 20% [69].

Even when a long follow up period is considered (15 years), no significant differences were found between patients undergoing ovarian-preserving surgery and those undergoing radical surgery in terms of risk of recurrence and death as Birge *et al.* [70] showed in a retrospective study of 66 patients with early-stage epithelial ovarian carcinoma.

Swift *et al.* [71] published a retrospective study on 31 patients with grade 1-2 endometrioid ovarian cancer FIGO-stage I concluding that ovarian preservation can be a well tolerated alternative for this subgroup of women. Of these patients, 35.5% underwent conservative surgery and 64.5% conventional treatment. The 5-year recurrence-free survival and the 5-year OS were 90.9 and 100% for patients in the conservative group and 84.0 and 92.6% for patients treated with conventional surgery (no significant difference) [71].

Regarding mucinous tumors, no differences in DFS were found if patients with early-stage ovarian cancer treated with radical surgery or with the preservation of the uterus and at least part of one ovary in the study by Lin *et al.* [72]; a tendency towards poorer DFS, however, was found in the infiltrative compared with the expansile pattern. These results suggest to carefully assess the pattern of presentation before offering conservative options to patients with diagnosis of mucinous histology [72].

Whether ovarian conservation could be considered in patients with clear cell ovarian carcinoma is still a matter of debate due to the reported high recurrence rates and resistance to chemotherapy. International guidelines do not recommend ovarian-sparing surgery for these women [64,65,69]. In a recent review conducted by Prodromidou *et al.* [73], five studies involving 60 patients with early-stage clear cell ovarian cancer were analyzed. Their results suggested that there was no significant difference in terms of survival and recurrence rates between

patients who underwent preservation of one ovary and those who had radical surgical procedures [73]. However, larger-scale studies are needed to assess the safety of ovarian conservation in patients with clear cell ovarian carcinoma.

Nonepithelial ovarian cancer

Malignant ovarian germ cell tumors (MOGCT) represent 1–4% of ovarian malignancies and are typically found in adolescents and young women often diagnosed at FIGO-stage IA [74]. MOGCTs have a favorable prognosis, with a 5-year survival rate of 94% for early-stage cases and an overall 5-year survival rate of 84% [75]. For patients with MOGCTs, FSS is considered the standard of care and should be performed regardless of the stage, as these tumors often respond well to chemotherapy [76]. Zamani *et al.* [77], in their retrospective study on 72 patients with MOGCT, showed that FSS with adjuvant chemotherapy is a well tolerated treatment and results in a high fertility rate even in patients with advanced stage disease.

Sex cord-stromal tumors (SCSTs) account for approximately 7% of ovarian malignancies, with an average age of diagnosis at 50 years. Among these, Sertoli-Leydig tumors or juvenile-type granulosa cell tumors are often diagnosed between the ages of 10 and 30, making them potential candidates for fertility-sparing surgery [78]. About 57% of malignant SCSTs are diagnosed at FIGO-stage IA, which carries a favorable prognosis [79]. The ESGO-ESMO guidelines recommend fertility-preserving surgery, which involves unilateral salpingo-oophorectomy and comprehensive surgical staging, as an option for patients with FIGO-stage IA SCSTs [62].

Sun *et al.* [78] showed in a retrospective study how unilateral ovarian preservation and uterine-sparing surgery can be considered for patients with FIGO-stage I SCSTs with reproductive needs, but they stressed the importance of long follow-up period (should not be less than 15 years). Particularly, for patients with stage IC disease, fertility-sparing option should be carefully selected, and close follow-up is necessary [78]. Despite the ovarian preservation, in malignant nonepithelial ovarian cancer, a complete surgical staging should be achieved. Incomplete surgical staging is considered a high-risk factor for shorter DFS in these patients. In a multicenter retrospective cohort of 107 patients, of whom 54 (50.5%) women underwent ovarian preservation and 53 (49.5%) received radical surgery, there was no significant difference in DFS between the two groups. Moreover, stage IC, tumor diameter more than 8 cm, incomplete staging surgery, and no adjuvant chemotherapy were the four

Table 3. Summary of current evidence for ovarian conservation in gynecologic cancers

Type of cancer	Potential candidates for ovarian conservation	Major risk factors for ovarian metastasis/recurrence
Endometrial cancer	<p><i>Best candidate:</i> FIGO stage IA grade 1-2 endometrioid histology aged ≤ 40 years</p> <p><i>Potential candidate:</i></p> <ul style="list-style-type: none"> - FIGO stage IA grade 3 endometrioid histology - FIGO stage IB grade 1-2 endometrioid histology - FIGO stage IA grade 1-2 endometrioid histology aged 41–45 years 	<p>age > 45</p> <p>myometrial invasion $> 50\%$</p> <p>cervical invasion</p> <p>pelvic lymph node metastasis</p> <p>nonendometrioid histology grade 3</p> <p>extrauterine disease</p> <p>presence of LVS1</p> <p>malignant peritoneal cytology</p>
Cervical cancer	Tumors < 4 cm confined to the cervix, with no evidence of lymph node metastasis with squamous cell carcinoma and HPV-associated adenocarcinoma	<p>adenocarcinoma (or adenosquamous) histology</p> <p>parametrial involvement</p> <p>uterine corpus tumor involvement</p> <p>pelvic/para-aortic lymph node metastasis</p>
Ovarian cancer	<p><i>Epithelial:</i> FIGO IA-IC grade 1-2 serous, endometrioid, mucinous expansile pattern</p> <p><i>Nonepithelial:</i></p> <ul style="list-style-type: none"> - Germ cell ovarian tumors: any stage - Sex cord-stromal tumors: FIGO IA 	<p>high grade</p> <p>advanced stage</p> <p>clear cell histology</p> <p>mucinous tumor with infiltrative pattern</p>

high-risk factors associated with a shorter DFS [80]. Also, in the study by Wang *et al.* [81], incomplete staging was associated with an increased risk of recurrence.

Comment

Unilateral ovarian preservation in patients with ovarian cancer added to uterine-sparing surgery can be considered in woman who desires to conceive. Women with epithelial ovarian cancer stage FIGO IA-IC with no risk factors (high-grade, advanced stage, clear cell, or mucinous tumor with infiltrative pattern) can be considered candidates for conservation of the nonaffected ovary, while for advanced stage, it is not a viable option due the high risk of recurrence. Unilateral salpingo-oophorectomy has to be preferred to cystectomy, as there is no evidence of safety for the latter. For patients with MOGCTs, FSS can be considered the standard of care also in advanced stage. Patients with SCSTs could be candidate to ovarian sparing surgery in case of FIGO-stage IA, particularly if surgical staging is complete, while careful selection and close (long-period) follow up must be done for FIGO-stage IC.

Table 3 demonstrates a summary of current evidence for ovarian conservation in gynecologic cancers.

CONCLUSION

Ovarian conservation is a surgical approach that involves preserving one or both ovaries during the

treatment of gynecologic cancers. This approach has gained popularity in recent years in two circumstances. First, ovarian preservation is a component of fertility preserving management. Second, preserving the ovarian endocrine function if fertility preservation is impossible or not wanted as major component of quality of life. The decision to perform ovarian conservation depends on several factors, such as the stage and type of cancer, the patient's age, and fertility goals. It is important to note that while ovarian conservation may offer certain benefits, particularly by protecting from consequences of early menopause, and preserving the androgen production after the menopause may be associated to a risk of cancer recurrence. Therefore, the decision to remove or spare the ovaries should be made by the patient after comprehensive counseling about the benefits and risks. Close monitoring and follow-up care are necessary to ensure the best possible outcomes for patients with gynecologic malignancies.

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Conflicts of interest

None.

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