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Fertility sparing surgery in gynecological cancers: A review of current state

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Abstract

Options for preserving fertility sparing surgery (FSS) in early-stage gynecological cancers are becoming more widespread as evidence supporting acceptable oncological and reproductive outcomes in well-selected patients continues to grow. It is crucial to thoroughly evaluate individuals' fertility potential before selecting surgical options. Fertility-sparing treatment of endometrial cancer (EC) is considered in cases confined to the endometrium. Hormone therapy is considered an absolute treatment and hysteroscopic resection, particularly using the 'grasping' technique, is a preferred method. Cervical cancer (CC) is usually diagnosed in patients during their reproductive years, hence FSS is extremely crucial for their treatment. Patients with early stage, low-risk CC and a tumor size ≤ 2 cm, have FSS options are available for preserving their fertility, including conization or simple/radical trachelectomy with pelvic lymph node assessment. A vaginal, abdominal, or minimally invasive approach can be used to perform a trachelectomy. Epithelial ovarian cancer (EOC) rarely allows for FSS; however, it may be considered in specific cases, such as stage IA low-grade tumors. Unilateral salpingo-oophorectomy (USO) and comprehensive surgical staging are integral components of FSS in EOC. Non-epithelial ovarian cancers, including germ cell tumors, are common in young women, FSS is the main treatment option. Borderline ovarian tumors (BOT) present challenges due to recurrence risks, and the choice between cystectomy and salpingo-oophorectomy is discussed.

Keywords: fertility sparing surgery, endometrial cancer, ovarian cancer, fertility preservation

1. Introduction

The standard treatment for many patients with gynaecological malignancies is removal of the reproductive organs, and a significant proportion of these patients will subsequently receive chemotherapy or radiotherapy with gonadotoxic effects. The treatments applied for gynecological malignancies observed in women of reproductive age have a negative impact on fertility in a significant portion of patients. Fertility-sparing surgery (FSS) options are available for early-stage gynaecological cancers, allowing women to limit potential reproductive damage and preserve their future fertility. With the increasing trend to delay childbearing in the modern world, the need for FSS in oncological is growing. Assessing the patient's suitability for FSS and determining the risks associated with potential reproductive and oncological outcomes are critical to management. FSS, in which the ovaries, uterus and sometimes part of the cervix are partially preserved, is used in selected cases of early-stage cervical, ovarian and endometrial cancers in women.

The aim of this review was to summarize the most recent and current status of FSS for gynaecological malignancies, including endometrial, ovarian and cervical cancer.

2. Endometrial cancer and fertility

Endometrial cancer (EC) is known as a disease of the postmenopausal period, with only approximately 4% of patients receiving a diagnosis of EC before the age of 40 (1). The preservation of fertility is expected to yield a favorable prognosis for young EC patients, as they often present with early-stage and low-grade tumors (2). As it is known, nulliparity is among the risk factors for EC and whether this association is due to infertility is unclear. The increasing frequency of EC in young patients and their strong desire to preserve fertility have drawn attention to conservative treatments, prompting further research.

In the selection of patients for fertility preservation in EC, important parameters include the patient's desire for pregnancy, age, suitability of reproductive potential, overall health, and body mass index. Fertility-sparing treatment of EC is considered in cases of grade 1, stage IA EC with no myometrial invasion and no risk factors for oncological safety (EC cases confined to endometrium confirmed by imaging). Hormone therapy is considered an absolute treatment and is therefore suitable for patients with no contraindications, making it a fertility-sparing option. There is insufficient data for patients beyond these limits and decisions should be made

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on a case-by-case basis (3).

A diagnostic biopsy for EC is mostly performed via dilatation and curettage (D&C) or pipelle. Biopsies taken without visualization has long been considered the standard method for obtaining a histological diagnosis. Biopsies taken without visualization of such lesions may sample less than half of the endometrial cavity (4). Therefore, a visual-focused hysteroscopic approach to endometrial diagnosis is emphasized to improve diagnostic accuracy (5, 6). Hysteroscopy not only provides a diagnostic advantage by better localizing the lesion, but also allows complete resection of the lesion.

3. FSS modalities in EC

3.1. Hysteroscopic resection

The surgical treatment of early stage EC, including patients who do not respond to initial progesterone therapy, is hysteroscopic resection (7, 8). The most widely accepted method is the hysteroscopic 'grasping' technique, which allows a larger and deeper portion of endometrial tissue to be removed (9). It is often preferred to the 'punch' method because it extracts more tissue. In Fig. 1, we can see the difference in tissue sample size between the hysteroscopic grasping technique and the punch technique (9). Therapeutic efficacy is based on removal of the tumour and subsequent enhancement of the potential pathological response required for effective hormone therapy. The addition of hormone therapy, primarily progesterone, to the resection treatment is associated with better hysteroscopic resection outcomes. The 'grasp' method, especially in the presence of an endometrioid-type tumour, provides more correlated results between histological type, myometrial invasion and tumour grade, leading to a better determination of prognosis (3). For safety, the spread of malignant endometrial cells into the peritoneal cavity during hysteroscopy does not change the stage of EC and does not affect the prognosis of the patient (10).

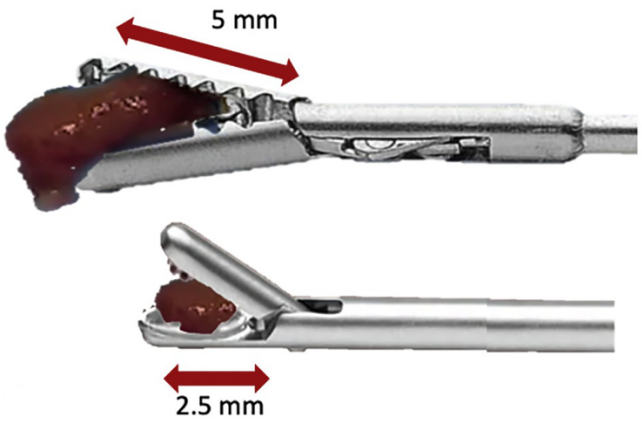

Fig. 1. Comparison of tissue sample sizes: Hysteroscopic grasping vs. Punch technique

3.2. FSS for cervical cancer

Cervical cancer (CC) is most commonly diagnosed in women between the ages of 35 and 44 (11), making fertility-sparing options even more important for this disease. Factors such as the patient's desire to preserve fertility, age and associated reproductive potential are important considerations. Factors that may limit fertility-sparing surgery include tumour size greater than 2 cm, non-squamous histopathology, positive lymph nodes, and cases with tumour-free margins less than 5 mm; as these are associated with a high risk of cervical cancer recurrence and lower oncological safety. Therefore, conservative surgery may not be preferred in such cases (12).

Options for patients who are suitable candidates for FSS and who want this approach include cervical conization, simple trachelectomy and radical trachelectomy.

3.3. Cone biopsy and simple trachelectomy

Cone Biopsy and simple trachelectomy can be an option in patients with FIGO Stage IA1to stage IB without lymphovascular invasion (LVSI) (13). In individuals with fertility preservation goals and LVSI negative cervical cancer, the risk of parametrial involvement is less than 1%. Therefore, conization and/or simple trachelectomy can be performed without parametrectomy (14). In stage IA1 CC cases with positive LVSI, conization or trachelectomy alone may not be sufficient and the addition of pelvic sentinel lymph node (SLN) mapping/lymphadenectomy is an appropriate approach.

The purpose of conization is to remove the ectocervix and endocervical canal as a whole. The National Comprehensive Cancer Network (NCCN) recommends cold knife conization as the preferred approach to conization. However, in cases where there is no electrocautery artefact and an intact and sufficient surgical margin can be achieved, loop electrosurgical excision procedure (LEEP) with the addition of endocervical curettage can be used as an alternative to conization. A preferred length for cold knife conization is at least 10 mm, and in patients with fertility expectations, an increase in this length is associated with adverse pregnancy outcomes (13). Less radical procedures have been associated with better obstetric outcomes in the literature (15). Radical trachelectomy is the most common fertility-sparing procedure for CC. However, studies have shown that for individuals with tumours smaller than 2 cm, conization or simple trachelectomy may be sufficient due to similar oncological safety and efficacy rates(15-17).

A simple trachelectomy is the removal of the entire cervix. Trachelectomy can be performed abdominally or vaginally. The choice of procedure for FSS for CC depends on stage, lesion size, lesion location, and individual surgical skills and preferences. The procedures used for CC are shown in Fig. 2.

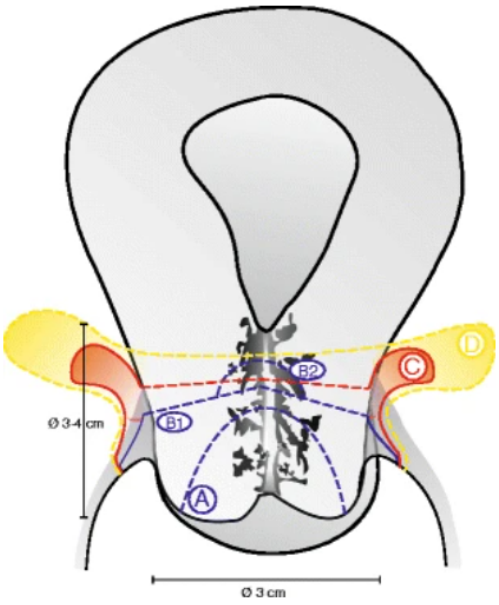

Fig. 2. Procedures for cervical cerclage

3.4. Radical Trachelectomy

Radical trachelectomy is a procedure in which the entire cervix together with part of the parametrium is removed either abdominally or vaginally. It is a preferred method for cervical cancer stage IA2 to IB1 due to its suitability for oncological safety.

Vaginal Radical Trachelectomy (VRT), also known as the Dargent procedure, refers to a transvaginal resection of the diseased cervix with 1 to 2 cm of vaginal mucosa and parametrium. Excision is performed leaving at least 1 cm of healthy tissue around the tumour and at least 1 cm of cervical stroma should be preserved at the internal cervical os (18). Afterwards, the anastomosis between the isthmus and upper vagina preserves the fertility and a prophylactic cerclage is then placed just above the margin using non-absorbable polypropylene or mersilene type suture to contribute positively to potential pregnancy outcomes. The procedure begins with laparoscopic pelvic lymph node assessment. The exclusion of nodal disease prior to FSS is crucial for patient selection. While NCCN guidelines recommend SLN mapping in patients with FIGO 2018 stage IA1 with LVSI and stage IA2-IB1 cervical cancer, data from prospective studies like SENTICOL I and SENTICOL II indicate that there is insufficient oncologic evidence regarding safety (13, 14).

For patients with tumours larger than 2 cm, VRT should not be preferred as there is a higher risk of recurrence. In a systematic review, the recurrence rate was 17% when VRT was performed for tumours larger than 2 cm, compared with 4% for stage IB patients with tumours of 2 cm or less (16). Abdominal radical trachelectomy (ART) allows a wider resection of the parametrium compared to vaginal surgery and is often preferred in women with stage IB1 >2 cm tumours in CC. In VRT, only the vaginal branch of the uterine artery is divided, whereas in ART the uterine arteries are divided from their origin at the hypogastric arteries. As in type III radical hysterectomy, complete ureteral dissection is performed through the parametrial tunnel, the posterior cul-de-sac is incised, and the uterosacral ligaments are divided. The vaginectomy is performed with an anterior colpotomy and the proximal specimen is excised approximately 5 mm from the internal os, followed by frozen section analysis. Although not routinely used, a prophylactic cerclage is placed abdominally at the level of the isthmus.

Although radical trachelectomy can be performed by minimally invasive route, the first prospective randomized trial comparing open and minimally invasive radical hysterectomy for cervical cancer (LACC) in 2018 showed that minimally invasive approaches were associated with worse disease-free and overall survival compared with open surgery. Therefore, concerns remain about the oncological safety of minimally invasive radical trachelectomy (19). However, the impact of minimally invasive radical trachelectomy on survival is not known from the available data and a definitive judgement on its use is not possible at this time (14).

A systematic review compared the surgical, oncological and obstetric outcomes of vaginal, abdominal and laparoscopic radical trachelectomy. Vaginal surgery had a shorter operative time and fewer positive surgical margins than abdominal and laparoscopic surgery. Vaginal surgery also had the highest pregnancy rate and lower rates of early delivery than the other two groups (20). Short-term and long-term postoperative morbidity is higher with ART than with VRT. Short-term complications such as bleeding and infection are more common with ART than with VRT (21, 22). In addition, long-term complications related to the radical nature of ART, such as ovarian failure due to uterine and ovarian artery ligation, cervical stenosis and Asherman's syndrome, are more common with ART than with VRT. In addition, complications related to the failure of the ART procedure are more common (23).

Neoadjuvant chemotherapy (NACT) is an alternative option for CC patients who often have tumours larger than 2 cm and want to preserve their fertility. NACT is given to shrink the tumour, allowing those who respond well to become candidates for FSS. While some studies suggest that lymph node dissection should be performed after NACT, it seems more appropriate to perform it before NACT, as positive nodes are associated with a poor prognosis and these patients need adjuvant treatment (14).

3.5. FSS in Ovarian cancer

Epithelial ovarian cancer (EOC) is the most lethal

gynaecological malignancy and is often diagnosed at an advanced stage. The median age at diagnosis is around 63 years and more common in older than younger women (24). Most patients with EOC undergo radical surgery in advanced stages, including hysterectomy and bilateral salpingo-oophorectomy, and fertility-sparing surgery is not recommended in these patients. In patients with EOC, FSS may be considered in a very limited group of patients, specifically those with stage IA low-grade serous, mucinous or endometrioid tumours. In addition, FSS could be offered to patients with stage IC low-grade disease (25) .

FSS in EOC consist of unilateral salpingo-oophorectomy (USO), omentectomy, pelvic and para-aortic lymphadenectomy, peritoneal washings and peritoneal biopsies. The entire abdomen should be examined and biopsies taken from suspicious areas. Endometrial biopsy should be performed to exclude synchronous EC, especially in endometrioid type ovarian cancer (26). Laparoscopic surgery can be used in a highly selected group of patients with EOC. The main concern with laparoscopic surgery is the risk of intraoperative rupture and spillage of the malignant tumour. Intraoperative rupture of the ovarian cancer may affect the staging of the EOC. Another disadvantage for laparoscopic surgery is the risk for metastasis at the port sites (27).

Non-epithelial ovarian cancers (NEOC) account for approximately 10% of all ovarian cancers and include germ cell tumours (GCT), sex cord-stromal tumours (SCST) and some rare tumours within the NEOC category (28). GCTs are usually diagnosed at an early stage, and as patients are often children or young women, FSS is the main treatment option. USO is often performed on the affected ovary and may be performed if there is a significant abnormality, taking into account the risk of adhesions or ovarian insufficiency. In addition, the peritoneal surfaces, omentum and lymph nodes are thoroughly examined and, if suspected, resected. If present, peritoneal lavage or fluid sampling should also be performed during surgery (29, 30). Malign GCTs are mostly unilateral, but in 10-15% of cases, pure dysgerminoma can be bilateral. Biopsy from the apparently normal contralateral ovary is not recommended due to the increased risk of peritoneal adhesions and a potential cause of mechanical sterility. Although oncological safety may not be as high as with USO, cystectomy may be considered as a treatment option in selected cases. (31).

Borderline ovarian tumours (BOT) have nuclear abnormalities and increased mitotic activity. They are distinguished from EOC by their non-infiltrative growth pattern and lack of stromal invasion. The majority of BOTs are diagnosed at stage I. They account for approximately 10-20% of all ovarian tumours, and about one third of these tumours are diagnosed in individuals under the age of 40. FSS is widely accepted in the treatment of BOT (32). While FSS in BOTs does not affect overall survival, the risk of disease recurrence is significantly increased, especially in cases of cystectomy (33, 34). Studies also suggest that USO is more effective than cystectomy in cases of positive surgical margins and incomplete resection (35). Therefore, despite the risk of malignant transformation, it is a reasonable option for patients with fertility expectations.

Regarding the route of surgery, studies have shown that the likelihood of cyst rupture is higher with laparoscopic surgery than with laparotomy; however, there is only a minimal difference in recurrence rates compared with open surgery (36). Peritoneal lavage, omentectomy and resection of clearly visible metastases are components of staging surgery. Routine lymph node dissection is not recommended in BOT. Lymphadenectomy in BOTs is only indicated if suspicious lymph nodes are identified on imaging or exploration during surgery (37).

Conflict of interest

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Authors' contributions

Concept: U.A., Design: U.A., Data Collection or Processing: U.A., Analysis or Interpretation: U.A., Literature Search: U.A., Writing: U.A.

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