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SPECIAL ARTICLE

Fertility Preservation Strategies in Gynecologic Cancers

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ABSTRACT

The incidence of most gynecologic malignancies significantly reaches their peaks after the age of 50, a substantial number of women encounter the diagnosis of gynecologic cancer during their reproductive year. Thus, fertility preservation has an important role in good quality of life in adolescents and young adults. The gynecologic oncologists should thoroughly discuss the potentiate infertility with all patients and refer them to reproductive specialists as earliest as possible to broaden the fertility preservation options and reduce decisional regret. There are roles of fertility preservation treatment in appropriately selected patients such as early stage cervical cancer (IA1-IB1), early stage of endometrial carcinoma with well-differentiated endometrioid subtype, and some subtypes of ovarian cancer (epithelium ovarian cancer stage IA, epithelium ovarian cancer unilateral stage IC, malignant ovarian germ cell tumor, sex-cord stromal tumor, borderline ovarian tumor) which the fertility preserving procedure yields the optimal oncologic outcomes and acceptable obstetrics result. Patients should be insistently informed that the fertility sparing treatment is not the standard of care and accepted possibilities of impaired survival. The doctors should emphasize comprehensive surveillance and a complete surgical staging following family completion must be achieved.

Keywords: fertility sparing, gynecology cancer, fertility preservation.

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Although the incidences of most gynecologic malignancies significantly reach their peaks after the age of 50, a substantial number of women encounter with the diagnosis of gynecologic cancer during their reproductive years. In the United States, out of the 113,520 women estimated to be diagnosed of female genital tract cancer in 2020, 21% was younger than 40 years[1]. In combination with the increasing sociodemographic transition towards women having their first childbirth beyond age 35, reproductive aging, and gonadotoxic treatments, fertility issues have become more frequent and complicated in women with cancer. Accordingly, the ultimate goals of oncologic treatment have expanded from the more survival to the

improved quality of life after surviving cancer[2]. Preservation of fertility play an important role of good quality of life in adolescents and young adults[3]. The objectives of this clinical review were to summarize and update in fertility preservation approaches.

Bases on the guidelines from the American Society of Clinical Oncology and the American Society for Reproductive Medicine, the oncologists should thoroughly discuss the potentiate infertility with all of the patients and refer them to the reproductive specialists as earliest as possible[4, 5]; as the prompt referrals broaden the fertility preservation options. The patients receiving pretreatment fertility preservation counselling experience less decisional regret in spite of their decisions to forego fertility preservation treatments. However, even with these recommendations, the referral rates to the reproductive specialists remain low[6, 7]. The contents should cover the variations in types of cancer, available time to the onset of the treatment, extents of the surgery, types and dosages of chemotherapy, types and dosages of radiation and the risk of sterility with the given treatments.

Fertility preservation strategies in gynecologic cancers

Female fertility is at risk following surgery, chemotherapy, or radiotherapy treatment for cancer(8). Ovarian damage from drugs is type and dose dependent and is related to the patients' age at the time of the treatment, while the progressively smaller doses can also cause ovarian failure as the patients' age. Total body, abdominal, or pelvic irradiation probably leads to ovarian and uterine damage, based on the radiation dose, fractionation schedule, and age at receiving the treatment[9]. An increased serum follicle-stimulating hormone (FSH) level is commonly used to indicate ovarian damage and failure. However, anti-mullerian hormone (AMH) and antral follicle count (AFC) are now comprehensively applied as other biochemical indicators of ovarian aging. For female cancer patient, fertility should be evaluated on a basis of a complete history, a thorough physical examination, laboratories and pelvic ultrasound[10]. Nevertheless, the most significant predictor of the reproductive potential and live birth rates is the patient's age. The recommended steps to approach each patient are as follows.

Comprehensively taken the medical, gynecologic, and surgical history

- Detailed menstrual history (menarche, cycle interval and length, and presence of ovulation)
- Obstetric history (gravidity, parity, time to previous pregnancies, and mode of delivery)
- History of prior fertility testing or treatment
- Partner reproductive history

Physical examination

- Vital signs, body mass index
- Thyroid gland
- Breast
- Pelvic examinations (uterine size, shape, position, adnexal masses, or tenderness)

Transvaginal ultrasound examination

- Uterine characteristics
- AFC (total number of small follicles that measure between 2-10 mm. in diameter on an early follicular phase), ovarian volume

Biochemical measures of ovarian reserve

- Serum FSH, estradiol, and inhibin B (measured in the early follicular phase)
- AMH

Fertility preservation options

1. Embryo cryopreservation

In the past, embryo cryopreservation was the sole alternative for the female cancer patients wishing for fertility preservation. Its limitation is the requirement of a specified partner contributing to fertilization the sperm with eggs.

2. Oocyte cryopreservation

The patients without a partner, refusing donor sperm or embryo cryopreservation may opt for ovarian stimulation and oocyte retrieval which freeze the eggs to be subsequently thawed. Lately, many institutes increase the pregnancy rates from using cryopreserved and warmed oocyte using cryoprotectants and cryotools

along with rapid cryopreservation technique (vitrification) and fertilization with intracytoplasmic sperm injection (ICSI)[11, 12]. Based on the available data, the Practice Committee of the Reproductive Medicine, recommended ovarian cryopreservation for the women, with high potential of ovarian failure, who are not candidate for embryo cryopreservation[13].

3. Ovarian tissue cryopreservation

At the moment, it is the only feasible option for prepubertal girls and the patients who must immediately start their chemotherapy or radiation treatment with inevitable delay[14]. However, the ischemic damage to the tissue pending the transplant and revascularization, not to mention the theoretical exposure to occult malignant tumor cells. If these obstacles are overcome, ovarian tissue preservation can facilitate the prompt treatment, avoidance hormonal use to stimulate the ovaries in the patients who can appropriately undergo laparoscopic ovarian biopsy or oophorectomy. Ovarian function usually returns within 2–8 months post-transplant and remains up to 7 years[5]. There are some controversies; still, a recent meta-analysis in 2017 reported as high as 37.7% cumulative live birth rate following ovarian tissue cryopreservation[15].

4. Ovarian transposition

If the patients require pelvic irradiation for their cancer, ovarian transposition (oophoropexy) is among other choice to be considered. Unfortunately, due to undeniable radiation scatter, ovaries may not completely survive and the thoroughly informed of the possible failure, from the systematic review, 67% of the cervical cancer patients undergoing ovarian transposition have their ovarian function preserved, ranging from 16.6-100%[16].

5. Ovarian suppression with gonadotropin releasing hormone (GnRH)

Based on a study in breast cancer patients treated with chemotherapy, GnRH analogs may partially reduce chemotherapy-induced primary ovarian insufficiency in the patients under age 40. In contrast, a randomized trial reported no benefit in ovarian reserve protection, indicated by AMH and FSH as surrogate markers[17, 18]. There is still insufficient long-term data on the return of menstrual function, ovulation, and pregnancy rates following chemotherapy in patients receiving GnRH analogs and further studies are needed to comprehensively determine the advantages of this medication in term of fertility and/ or endocrine function preservation[5].

Fertility sparing by cancer site

1. Cervical cancer

Cervical cancer is commonly diagnosed in reproductive age women, as high as 37% of the new cases are encountered in women below 45[19]. The following criteria should be met in the fertility sparing surgical candidates:

- Histologic type: squamous cell carcinoma, adenocarcinoma or adenosquamous histology
- Tumor size: lesion less than or equal to 2 cm
- Other risk factors: no deep stromal invasion
- No evidence of lymph node involvement
- No distant metastatic disease

According to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging of cervical cancer, the clinically early-stage patient treatments are as follows[20].

1. Stage 1A1 with no lymphovascular invasion (LVSI): Cervical conization with negative margin at least 3 mm preferably a non-fragment specimen along with negative tissue from endocervical curettage. If the margin was positive, re-procedure or trachelectomy is recommended. The risk of recurrence after conization in patients with stage IA1 disease, with no LVSI, negative endocervical curetting after excision, and negative surgical margins was less than 0.5%[21].

2. Stage 1A1 with positive LVSI, stage 1A2: Radical trachelectomy with pelvic lymphadenectomy (considering sentinel lymph nodes (SLN) mapping in case of tumor size less than or equal to 2 cm) is recommended. Cervical conization with negative margin, a non-fragment specimen and negative tissue from endocervical curettage with pelvic lymphadenectomy can also be an option (considering SLN mapping in case of tumor size less than or equal to 2 cm). However,

in the patients with positive LVSI, the risk of recurrence may increase up to 9%, necessitating the pelvic lymph node dissection with the recommended SLN mapping.

3. Stage 1B1: Radical trachelectomy with pelvic lymphadenectomy (considering SLN mapping in case of tumor size less than or equal to 2 cm) with or without paraaortic lymphadenectomy.

4. Stage 1B2 (in selected cases): From a systematic review, in the advanced cervical cancer with tumor size 2-4 cm, neoadjuvant chemotherapy with platinum-based regimen followed by fertility sparing surgery feasibly preserved the patients' fertility[22]. Nonetheless, the data is limited, and the high risk of recurrence (6%) raises the concerns in terms of the oncological safety. These options should cautiously be offered to the highly selected patients.

Radical trachelectomy with pelvic lymphadenectomy can be accomplished with the abdominal (AT), vaginal (VT) or minimally invasive approached (laparoscopy or robotic surgery). Nonetheless, cervical excisional procedures are notably associated with the substantially increased obstetric complications, such as preterm delivery and prematurity, mainly as a consequence of the loss of cervical anatomical support and physiological function. In addition, cervical stenosis is highly contributed to complicated procedures. Because the infertility rates following the procedures range from 14%–41%, assisted reproductive technologies (ART) are imperative to achieve pregnancy[23, 24].

A systematic review, focusing on the reproductive and oncologic outcome after fertility-sparing surgery for the early-stage cervical cancer endorsed this option as an alternative to the conventional radical hysterectomy in women desiring fertility preservation. The mean clinical pregnancy rate of patients who tried to conceive was 55.4%. The mean live birth rate was 67.9%, 20 percent of which required ART. Regarding the oncological issues, the mean recurrence rate was 3.2% and the cancer death rate was 0.6%, based on the median follow-up period of 39.7 months[25].

Before the fertility-sparing surgery for early-stage cervical cancer, the patients must comprehensively be informed of all intraoperative and postoperative findings that can possibly lead to the loss of fertility. Intraoperatively, if adequate margins and/or positive lymph nodes are encountered, the scheduled fertility sparing procedure will be fortified. Despite completion of the fertility sparing surgery, post procedurally, a small number of the patients will eventually need adjuvant chemoradiation based on their final pathological report, affecting the preserved uterus and diminish the chance to successful pregnancy[24].

2. Endometrial cancer (EC)

The overall incidence of EC has rapidly increased, especially in the proven under 40, who are unsurprisingly nulliparous and consequently, desire to maintain childbearing ability. Fortunately, young women are usually diagnosed in the early stages and low grade, possessing good prognosis. Besides the counselling on the standard treatment for EC, total hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic washing, with or without lymphadenectomy[26], for fertility-sparing consideration, the patients must be practically assessed potentiality of spontaneous conception in the context of such as chronic anovulation or polycystic ovarian syndrome, the feasibility and total cost of ART[27, 28]. Before considering fertility preservation, the following criteria should be fulfilled[29].

- Young women of child-bearing age (preferably under 40 years) diagnosed with endometrial cancer, stage IA.
- Well-differentiated tumors with < 50% myometrial invasion assessed by magnetic resonance imaging (MRI).
- No evidence of pathological lymph nodes (the risk of pelvic and paraaortic lymph node involvement is 4.7 and 1.7%, respectively)[30].
- No evidence of synchronous or metachronous ovarian tumors (adnexa involvement and ovarian coexisting neoplasm is 6 and 19%, respectively)[30].
- No family history or hereditary cancer syndromes, as evidenced by mutation testing primarily for Lynch syndrome by immunohistochemical staining of the tumor specimens for mismatch repair (MMR) proteins. The MMR deficiency in patient with endometrial cancer is linked with an increased rate of synchronous

or metachronous ovarian tumors (10-29%) and significantly worse progression-free survival (48.6% vs 83.3%), as well as overall survival (56.5% vs 90.0%)[31-33].

Even though the initial diagnosis is made by an office endometrial biopsy, dilation and curettage should still be performed for the sake of better determining cancer grade[34]. Hysteroscopic biopsy is also proposed because of the more accurate final pathologic examination in comparison with dilatation and curettage[35, 36]. Despite the tentatively higher rate of peritoneal cytology, the survival is not evidently impacted[37]. MRI examination is the best investigational tool to evaluate the extent of myometrium infiltration, with a sensitivity and a specificity of 74%(38). Alternatively, expert transvaginal ultrasound examination can be applied[39].

Hormonal treatment

At the present time, the regimens of hormonal therapy in fertility preserving treatment are not standardized, however, based on the well conducted studies, the recommendations are oral form alone or in combination with intrauterine system with or without GnRH analogs. Over more, the successful treatment depends on hormone receptor expression on cancer cells, with the response rate from 26% to 89% in estrogen and progesterone receptor positive tumors and as low as 8-17% in the receptor negative group[40, 41]. The advised management are as below.

1. Medroxyprogesterone acetate (MPA): 400–600 mg daily
2. Megestrol acetate: 160–320 mg daily
3. Intrauterine device (IUD): 20, 52 mg daily levonorgestrel (LNG) (combination with oral progestins with or without GnRH analogs)
4. GnRH analogs

In two systematic reviews recruiting patients with both atypical hyperplasia and stage I endometrial cancer given varies progestin-containing regimens, hormonal therapy yielded an acceptable complete response rate of 71–78%, with approximately one third of patients achieving pregnancy[42, 43]. Interestingly, this affected more evidently in, comparing with carcinoma (66% vs 48%). Unfortunately, upon follow-up of them with initial responses, 23% with hyperplasia and 35% with carcinoma encountered a recurrence. A meta-analysis including 1,038 women reported the higher pooled response rates in women using both the LNG-IUD and oral progestins, in comparison with LNG-IUD and oral progestins alone (87% vs 76% and 71%, respectively)[43]. In addition, there are other non-hormonal treatment options.

1. Hysteroscopic resection

The surgical technique pointing out a lesion which has a suspicious malignant characteristic was first reported by Mazzon et al[44]. From a meta-analysis in 2010, in combination with hormonal therapies, hysteroscopic resection was validated as an auspicious treatment with a regression rate of 100%; whereas the hormonal therapy alone and surgery alone achieved 49.6 and 75% regression rate, respectively[45]. Nonetheless, intrauterine adhesion possibly undeniably occurs[46].

2. Weight loss

Presently, the correlation between weight loss and risk reduction of recurrence increased survival in endometrial carcinoma patients lacks of high quality evidence, especially in terms of fertility sparing treatment[39].

3. Metformin

Metformin expresses the antineoplastic activity by stimulating multiple signaling pathways in cell metabolism[47] possibly interferes the estrogen mediated endometrial proliferation[48]. Metformin administration along with tentatively associates with an improved overall survival in patients with endometrial carcinoma and a reduced cancer relapse risk.

The appropriate follow-up schedule for women after hormonal treatment option for fertility sparing patients with endometrial cancer is not established. Based on the risk of endometrial cancer progression, office endometrial biopsy (possibly performed with an IUD in place) is recommended in some institutional protocols every 3 - 6 months, until two consecutive negative biopsies are noted, if a complete response is proved, conception should be authorized. Upon complete childbearing, definitive hysterectomy should be encouraged, owing to the evident long-term

recurrences[49].

When definitive surgical staging is indicated, ovarian preservation is justified in patients with early-stage, low-grade tumors with grossly normal appearing ovaries intraoperatively. A large database study confirmed the safety of ovarian preservation in women under age 50 at the time of endometrial cancer surgery for the benefits of maintain function which is related to the decreased risk of death from cardiovascular disease and improved overall survival[50, 51].

3. Ovarian cancer

Ovarian cancer is mostly diagnosed among postmenopausal women. Unfortunately, around 12% of the patients suffer with this disease during their reproductive years[52]. Surgical staging which consists of hysterectomy, BSO, omentectomy, peritoneal washings, and pelvic and para-aortic lymphadenectomy is the standard treatment. The pathology of the tumor is normally not obtained until after the operation, leading to more diagnostic challenges than endometrial and cervical cancer. Therefore, any patients with an adnexal mass should undergo a thorough preoperative evaluation, comprising imaging studies and tumor markers. Intraoperative decision-making is critical and relies on an operative findings and frozen section. In addition, a patient must understand that frozen section pathology may be different from the final pathology and a two-step procedure is inevitable in some conditions[53, 54].

Currently, the consensus on the criteria for conservative approach is not settled but according to current evidence and recommended guideline, fertility sparing surgery can be opted subjecting to the histology and disease stage[55]. A fertility sparing surgery probably consists of an ovarian cystectomy or unilateral salpingo-oophorectomy (USO), omentectomy, peritoneal washings, pelvic and paraaortic lymphadenectomy, and peritoneal biopsies, preserving of the uterus and contralateral ovary. The routine biopsy of a normal appearing contralateral ovary is not recommended. The diverse extent of the necessary steps of the procedure is decided by the ovarian tumor histology.

3.1. Epithelium ovarian cancer

A large cohort study based on the US National Cancer Database revealed no association between fertility sparing surgery in stage IA or unilateral stage IC epithelial ovarian cancer and an increased risk of death, comparing to conventional surgery. However, the number of patients with high-risk histology were comparatively low[56], the safety of fertility sparing surgery in patients with high-risk features, such as stage IC disease or other high grade histology raised some concerns[57, 58]. The patients with stage IC epithelial ovarian cancer or other high-risk features should be conscientiously informed of the limited oncologic safety data. The recommended procedures are USO and comprehensive surgical staging (peritoneal sampling, omentectomy, pelvic and para-aortic lymphadenectomy) if the lesion is encapsulated, well differentiated and unilateral disease, with no extra ovarian metastasis, adhesion or ascites[59]. The previous studied of the reproductive outcome demonstrated the average pregnancy rate of 36% with 82% live birth[41].

3.2. Borderline ovarian tumors (BOT)

Accounting for 10% to 20% of the overall ovarian epithelial tumors, the incidence of BOT is 1.8 to 4.8 per 100,000 women per year[60], which is rising, especially in the patients in childbearing age[61, 62]. In the women with fertility desire, the surgical management is limited to USO with complete surgical staging (abdominal cavity exploration, peritoneal washing, infra-colic omentectomy, multiple peritoneum biopsies)[59], on condition that the disease is confined to a single ovary[63]. Ovarian cystectomy is acceptable, providing that the patients must realize that the recurrence rates are greater than 30%. If there is bilateral ovarian involvement and complete resection can be accomplished, ovarian cystectomy is the treatment of choice[64]. Based on the 2020 prospective study, the overall recurrence rate was 1.1% in FIGO stage I and 25.5% in FIGO stage III-IV. The relapse of all BOT was 13.7%. The significant risk factors for recurrent disease are FIGO stage III-IV and fertility sparing surgery[65].

3.3 Sex-cord stromal tumor (SCSTs)

SCSTs was diagnosed in 7% of the ovarian cancer patients, and the mean age at diagnosis is 50 years. However, Sertoli Leydig tumor or juvenile-type granulosa cell tumor are often encountered between ages 10 years and 30 years, who may be candidates for fertility preservation[66]. Approximately 57% of the malignant SCSTs are stage 1A, with a promising prognosis. The National Comprehensive Cancer Network (NCCN) guidelines[63] suggest the fertility sparing option, which includes USO and comprehensive surgical staging (the requirement of complete bilateral pelvic and para-aortic lymphadenectomy is not settled.)[59] for FIGO stage IA and IC disease.

3.4 Malignant ovarian germ cell tumor (MOGCT)

Malignant germ cell tumors occur in around 1% - 4% of the ovarian cancer patients and are usually diagnosed in adolescents and young women, who are mostly in FIGO stage IA disease. MOGCT are associated with a highly favorable prognosis. It is evidently regarded with a 5-year survival rate as high as 94% for early-stage disease, and an 84% 5-year survival rate overall(67). For patients with MOGCT, thoughts to the chemo responsive nature of the tumors, the standard of care and should be performed, regardless of the stage(68), USO and comprehensive surgical staging (examination and palpation of the omentum and resection, examination and palpation of the iliac and aorto-caval nodes are recommended[59]. From a systematic review, the fecundity rate was 24.6% and 80% of the patients trying to conceive succeeded at least one pregnancy[69].

Summary

All newly diagnosed, early-stage gynecologic cancer patients who are in their reproductive years and classified as the candidates for fertility sparing treatments should be promptly referred to the reproductive specialists as soon as possible; since the initiation treatment planning. Early referral facilitates the patient's realization of her chance of fertility, as well as the factors that might affect it. In addition, the counselling provides the extensive details of the fertility preservation options and the available ART. Pre-treatment counselling substantially impacts the decision-making which is mainly based on the fertility risks from the treatments and an alternative in case of the failed conservative management. Patients should be insistently informed that the fertility sparing treatment is not the standard of care and accepted possibilities of impaired survival. The doctors should emphasize on a comprehensive surveillance and a complete surgical staging following family completion must be achieved.

Potential conflicts of interest

The authors declare no conflicts of interest.

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