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INVITED REVIEW ARTICLE

Fertility Sparing Surgery in Gynecologic Cancer

Rema P. · Ahmed Iqbal

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About the Author

P. Rema is now working as Associate Professor in Gynaeoncology Division of Surgical Oncology at Regional cancer centre, Trivandrum, Kerala. She has more than 10 years of experience in Gynecologic Oncology. Her areas of expertise include cytoreductive surgeries for cancer ovary, laparoscopic radical hysterectomies, laparoscopic pelvic lymph node dissections, and exenterative surgeries for cervical cancers. In addition to being in charge of the surgical care of gynecological cancers, she actively involved in screening programmes of the centre. She conducts colposcopy and precancer clinics where facilities for videocolposcopy, LEEP, cryotherapy, and cold coagulation are available. She is also involved in imparting training for gynecologists from district hospitals and medical colleges in gynae oncosurgery

Abstract Fertility preservation is one of the major concerns of young patients diagnosed with gynecological cancer. With newer treatment regimens and better surgical techniques, survival rates after cancer treatment have improved, hence preservation of fertility has recently become an important issue in the treatment of gynecological cancers. Fertility sparing surgery may be an option for early-stage cervical cancer with the development of loop excision techniques and radical trachelectomy which allows a radical approach to cervix cancer at the same time preserving the uterus and thus fertility. Fertility preservation is possible in Stage 1 epithelial ovarian cancers, germ cell ovarian tumors, and borderline cancers. Hormonal therapy with progestin agents is effective in early endometrial cancer. In patients desiring future pregnancy, fertility sparing options must be explored before starting treatment for gynecologic cancers.

Keywords Fertility sparing surgery · Gynecologic cancers · Fertility preservation · Hormonal therapy

Rema P. (✉), Associate Professor · Ahmed I.
Division of Surgical Oncology, Regional Cancer Centre, Trivandrum, Kerala, India
e-mail: drremaanil@gmail.com

Introduction

The diagnosis of cancer is a devastating news to a patient of any age but it is exceptionally so when it happens in a young lady who has not borne children who is diagnosed with gynecological cancer. This is because the treatment of gynecological cancer by surgery, chemotherapy, or radiation is going to result in permanent infertility. This is a very difficult clinical situation not just to the patient but to the treating clinician also who cannot compromise on treatment of cancer but at the same time has to take into consideration the patients wish to have a baby of her own.

Perhaps, this situation did not exist a few decades back when cancer was considered as a deadly disease and the whole emphasis of treatment was on eradicating cancer without taking into consideration other issues like fertility preservation. But now with newer treatment regimens, better surgical techniques, newer chemotherapeutic agents, survival rates of cancer have gone up, hence issues like fertility preservation have gained importance in the present scenario.

The effects of cancer treatment on female fertility were assessed by Schover et al. [1]. They found that fertility preservation was one of the major concerns of patients less than forty seeking cancer treatment. They were interested in having children despite serious concerns in it affecting cancer treatment. When cancer treatment resulted in permanent infertility, it resulted in great emotional distress and this was one of the major issues affecting the patient's long-term quality of life.

Fertility preservation surgery means retaining the patient's uterus and ovarian tissue enough to allow future conception. Literature shows that in properly selected patients with gynecologic cancers organ preserving surgeries gives equally good cure rates as radical surgery. But before embarking on fertility preserving surgeries, it is important to have long counseling sessions with the patient and her care takers. It should be explained to them what is the standard treatment for her cancer and what are the fertility preservation surgeries possible. She should also be made aware about the oncological risks she will be subjected to on resorting to fertility preserving surgeries and the subsequent likely need for reproductive technologies to ensure conception.

The three most common gynecological cancers are those of cervix, ovary, and endometrium. Hence we will confine our discussion to the role of fertility preservation in these three malignancies. Although these cancers are common in elderly patients, 40 % of cancer cervix, 12 % of cancer ovary, and 5 % of cancer endometrium occur in patients in reproductive age group. This coupled with recent trend in delaying age of first pregnancy has resulted in more patients seeking fertility preservation surgeries.

Cancer Cervix

Cancer cervix is the most common cancer affecting females in developing countries including India. In fact, India is contributing to one fifth of global burden of cervical cancer [2]. Although prevention, early detection, and treatment have all proven to be effective in controlling cervical cancer, this has not been fully utilized in our country resulting in a high burden of incidence and mortality from cervical cancer.

Early cervical cancer is traditionally treated by radical hysterectomy or chemoradiation which can result in permanent infertility. However, in selected patients with early cervical cancer, fertility preservation techniques can be used with reliable oncologic outcomes.

Fertility preservation is possible in early cervical cancer including cancer in situ, microinvasive cancer, and stage IB cancers less than 2 cm. Cervical intraepithelial neoplasia (CIN) and cancer in situ are precursors of invasive cancer and are effectively treated by loop electrosurgical excision procedure (LEEP). LEEP is done as an outpatient procedure with excellent cure rates and has replaced hysterectomy for treating CIN and cancer in situ [3].

Stage IA1 cancer cervix is microinvasive cancer with depth of cervical stromal invasion less than 3 mm. This is effectively treated by cervical conisation. A cone-shaped portion of cervix is removed with the base on the ecto cervix and apex 1 cm from internal os. Conisation is very effective in treating microinvasive cervical cancer but carries complications like cervical stenosis and increased risk of obstetric complications. Metaanalysis by Kyrgiou showed that cold knife conisation for early cervical cancer is associated with increased risk of preterm labor, premature rupture of membranes, low birth weight, and caesarian section rate [4].

In stage IA1 cervical cancer with lymph vascular space invasion, Stage IA2 cancers, and stage IB1 cancers less than 2 cm, the fertility preservation surgery is radical trachelectomy [5]. Radical trachelectomy removes the cervix with medial parametrium and upper 2 cm vaginal cuff retaining the uterus and adnexa to allow future pregnancy. Cervical cerclage is done at the level of isthmus using permanent sutures to prevent cervical incompetence. This surgery is based on the observation that cancer cervix spreads early to the parametrium and adjacent vagina and very rarely to the uterine fundus. This makes it possible to remove the cervix, parametrium, and upper vagina retaining the uterus and adnexa to allow conception. This surgery was popularized by Daniel Dargent in 1994. Now radical trachelectomy is a well established and safe fertility sparing procedure for early cervical cancer in women less than forty with a keen desire to preserve uterus [6]. Patient is preoperatively assessed by MRI to find out the tumor dimensions and depth of invasion. An ideal candidate should have a tumor less than 2 cm without deep cervical stromal involvement and lymph nodal metastasis. The patient is counseled about the oncological and obstetric problems after the procedure including the risk of permanent infertility. Radical trachelectomy is usually performed vaginally with laparoscopic pelvic lymphadenectomy but can also be done by abdominal route. The most common complications after the procedure are irregular bleeding, dysmenorrhea, isthmic stenosis, amenorrhea, and rarely deep dyspareunia [7].

Till 2012, 992 cases of radical trachelectomy have been reported in the literature with 439 successful pregnancies [8]. The oncological outcome was also good and the risk of recurrence being <3.5 % is comparable to radical hysterectomy. The rate of second trimester abortion was twice that of normal population due to ascending infection with premature rupture of membranes. The lack of cervical mucus during pregnancy is supposed to cause cervical incompetence and ascending infections. The patients need careful evaluation for cervical incompetence and antepartum management with prophylactic antibiotics.

Ovarian Cancer

Ovarian cancer is surgically treated by hysterectomy and bilateral salpingo oophorectomy, but fertility preservation is possible in germ cell cancers, border line tumors, sex cord stromal tumors, and even early epithelial ovarian cancers.

Germ cell ovarian tumors affect girls in their first or second decade of life. They present usually with early-stage disease and are always candidates for fertility preservation. The surgical staging includes unilateral salpingo oophorectomy with comprehensive surgical staging. Extra ovarian disease is effectively treated by chemotherapy with bleomycin, etoposide, and cisplatin (BEP). Although ovarian failure is a risk of chemotherapy, most of the patients after BEP regain menstrual periods and have good fertility outcome.

Borderline cancers also called low malignant potential tumors affect patients in reproductive age group and are effectively treated by fertility preservation surgery. Unilateral tumors need only unilateral salpingo oophorectomy. Rarely can they be bilateral and in such situations ovarian cystectomy preserving normal ovarian tissue is done. They also have good prognosis and excellent survival [9].

Sex cord stromal tumors also present in early stages and are treated by conservative surgery. They usually have good prognosis but late recurrences sometimes occur and hence they need prolonged follow up.

Unlike the above mentioned tumors, epithelial ovarian cancers are highly aggressive and are the most common cause of death among gynecological malignances. Although the disease affects elderly females, 3–17 % of tumors affect patients <40 years and 30 % patients present with stage I disease. In these patients, fertility preservation is possible for a limited group of patients with early-stage disease and favorable histology. American College of Obstetrics and Gynecology (ACOG) 2007 guide lines and European Society for Medical Oncology (ESMO) in 2008 recommend fertility preservation for stage IA cancer ovary, Grade 1 or 2 with non-clear cell histology [10–12]. Along with conservative surgery, a thorough surgical staging including pelvic and para aortic lymphadenectomy, multiple peritoneal biopsies, and omentectomy is performed. Intraoperative tumor spill is also taken as IC disease even when the tumor is confined to one ovary according to FIGO staging and hence all attempts should be made during surgery to deliver the tumor without spillage. There is varying reports on the risk of tumor spillage on patient survival, some authors reporting poorer survival after tumor spillage, while others contradicting the same [13–16].

There have been reports of conservative surgery being performed for IC and grade 3 disease but the available evidence to select patients for fertility preservation with higher stage disease and unfavorable histology is limited to retrospective studies in small number of patients and is not well defined in systematic reviews [12, 17].So, the treating gynecologist should have a thorough discussion with the patient and her relatives explaining the possible oncological risks and the expected benefits before deciding on fertility preservation for epithelial ovarian cancers of stage IC, grade 3, and clear cell histology. After fertility sparing surgery, if patient needs adjuvant chemotherapy as in IC and grade 3 cancer, this further compromises her fertility due to chemo-induced gonadotoxicity. The remaining ovarian tissue can be protected to some extent by hormonal down regulation using GnRH analogs or oral contraceptives.

Patients with hereditary syndromes which make them more susceptible to breast and ovarian cancers are also not suitable for fertility preservation. When uterus is retained in fertility sparing surgery, it is mandatory to have an endometrial biopsy especially in endometrioid ovarian cancer where there is a 15 % chance of coexisting endometrial cancer. A wedge biopsy from normal looking opposite ovary is not needed but if there is tumor in the opposite ovary it should be excised.

After fertility preservation surgery, patients are followed up with clinical examination, ultrasonogram, and tumor markers. Assisted reproductive techniques are safe in borderline and germ cell tumors but there is limited evidence of their use in epithelial cancers. Completion surgery after child bearing is usually not performed in germ cell and borderline tumors but in early epithelial cancers patient is given the option of close follow up or completion surgery.

Endometrial Cancer

Endometrial cancer is also a disease of postmenopausal age group but 25 % patients are premenopausal and 5 % are <40 years. These patients are usually obese and nulliparous with history of infertility. Endometrial cancer is present in early stage and has excellent prognosis with surgical staging which includes hysterectomy, bilateral

salpingo oophorectomy, and assessment of pelvic and para aortic lymph nodes. As the standard treatment for cancer endometrium is hysterectomy, fertility preservative option is hormonal treatment for women with early, low grade cancers. Retaining uterus for the sake of fertility may subject the patients to disease progression. Hence proper candidate selection is compulsory for fertility preservation.

Cancer endometrium in young patients occurs due to hyper estrogenic milieu. The precursor for cancer is usually atypical hyperplasia [18]. Atypical endometrial hyperplasia is effectively treated with high dose progestrones with a 94 % regression rate. High dose progestrones can also be given for early endometrial cancer if the tumor is well differentiated, of endometrioid histology and is confined to endometrium. An MRI scan helps to select candidates for uterine preservation. If the tumor is not infiltrating myometrium with no enlarged lymph nodes and no synchronous ovarian tumor, she can be given a course of high dose progestrones. Megestrole acetate 160 mg/day or Medroxy progesterone acetate 200–400 mg/day is continued for 9–12 months. Instead of oral progestrones, GnRH analogs are also effective. Levonorgestrel intrauterine devices (LNG IUD) considering their local effect on the endometrium with less systemic side effects are also effective in treating early cancer endometrium [19, 20]. Progestrones produce side effects including head ache, weight gain, thromboembolism, and depression. Progesterones are contraindicated in patients with history of thromboembolic disease, breast cancer, and hepatic dysfunction.

70 % of tumors respond to progestrones but 25 % relapse after initial response [21]. Patients need close monitoring considering the risk of disease progression. Ultrasound evidence of endometrial thinning is an indirect marker of response. But there are no data on the most accurate method of assessing the endometrial response to hormonal therapy. Endometrial aspiration biopsy, D&C, and hysteroscopic biopsy are the various methods used. Especially with the LNG IUD in the uterine cavity, the assessment of endometrial response is not reliable. In a recent study, Kim et al. [22] found that D&C after removal of LNG IUD is more accurate than endometrial biopsy with the intrauterine devise in situ.

In responders response to hormonal treatment occurs in 16 weeks. So, patients are reassessed after 4–6 months. These patients need definitive treatment after completion of family.

Conclusion

Preservation of fertility is an important concern in patients with gynecological cancer. Fertility sparing surgery is often possible in selected patients of cancer cervix, ovary, and endometrium. For fertility preservation, patients should be carefully selected and extensively counseled regarding the deviation from the standard of care, the oncologic risks, and the subsequent likely need for reproductive technologies to ensure conception.

Compliance with ethical requirements and Conflict of interest This is a review article and did not include study of patients, medical records or volunteers, so as per our institutional guidelines did not require the approval of Hospital ethical committee. P. Rema and Iqbal Ahmed declare that they have no conflict of interest.

References

1. Schover LR, Rybicki LA, Martin BA, et al. Having children after cancer: a pilot survey of survivors' attitudes and experiences. Cancer. 1999;86:697–709.
2. Ferlay J, Shin HR, Forman D, et al. Estimates of worldwide burden of cancer in 2008: Globocan 2008. Int J Cancer. 2010;127(12):2893–917.
3. Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC Press; 2003.
4. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet. 2006;367:489–98.
5. Martinez A, Poilblanc M, Ferron G, et al. Fertility-preserving surgical procedures techniques. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):407–24.
6. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. Eur J Surg Oncol. 2007;33:933–41.
7. Abu-Rustum NR, Sonoda Y, Black D, et al. Fertility-sparing radical abdominal trachelectomy for cervical carcinoma: technique and review of the literature. Gynecol Oncol. 2006;103:807–13.
8. Ribeiro Cubal AF, Ferreira Carvalho JI, Costa MF, et al. Fertility-sparing surgery for early-stage cervical cancer. Int J Surg Oncol. 2012;2012:936534.
9. Heinz APM, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. Int J Gynecol Obstet. 2006;95(Suppl 1):S161–92.
10. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: management of adnexal masses. Obstet Gynecol. 2007;110:201–14.
11. Aebi S, Castiglione M. Epithelial ovarian carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008;19(Supplement 2):ii14–6.
12. Menczer J. Conservative fertility-sparing surgical treatment of invasive epithelial ovarian cancer: when is it acceptable? IMAJ. 2013;15:116–20.
13. Vergote I, De Brabanter J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet. 2001;357(9251):176–82.
14. Higashi M, Kajiyama H, Shibata K, et al. Survival impact of capsule rupture in stage I clear cell carcinoma of the ovary in comparison with other histological types. Gynecol Oncol. 2011;123:474–8.
15. Bakkum-Gamez JN, Richardson DL, Seamon LG, et al. Influence of intraoperative capsule rupture on outcomes in stage I epithelial ovarian cancer. Obstet Gynecol. 2009;113:11–7.
16. Paulsen T, Kærn J, Tropé C. Improved 5-year disease-free survival for FIGO stage I epithelial ovarian cancer patients without tumor rupture during surgery. Gynecol Oncol. 2011;122(1):83–8.

17. Fotopoulou C, Braicu I, Sehouli J. Fertility-sparing in early epithelial ovarian cancer: a viable option? Obstet Gynecol Int. 2012;2012:238061.
18. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia: a long-term study of "untreated" hyperplasia in 170 patients. Cancer. 1985;56:403–12.
19. Montz FJ, Bristow RE, Bovicelli A, et al. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol. 2002;186(4):651.
20. Dhar KK, NeedhiRajan T, Koslowski M, et al. Is levonorgestrel intrauterine system effective for treatment of early endometrial cancer? Report of four cases and review of the literature. Gynecol Oncol. 2005;97(3):924.
21. Ramirez PT, Frumovitz M, Bodurka DC, et al. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133–8.
22. Kim MK, Seong SJ, Song T, et al. Comparison of dilatation & curettage and endometrial aspiration biopsy accuracy in patients treated with high-dose oral progestin plus levonorgestrel intrauterine system for early-stage endometrial cancer. Gynecol Oncol. 2013;130(3):470–3.