FERTILITY SPARING OPTIONS IN PATIENTS WITH GYNAECOLOGIC CANCERS
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Abstract
The incidence of cancers in young women is increasing, raising the issues of infertility with standard surgical treatment which consists of removal of uterus and adnexa in women who are nulliparous or have not completed their family. Fertility preservation options are available for early stage cancers of uterine cervix, endometrium, ovary. Counselling needs to be done regarding benefits of fertility preservation, cancer treatment versus risk of persistence, recurrence and metastases.

Conization and radical trachelectomy with or without lymphadenectomy is a well-established fertility sparing surgical option for young women with early stage cancer of uterine cervix. The role of fertility sparing surgery in endometrial cancer is limited. In women with germ cell tumors of ovary and border line ovarian cancer, fertility preservation can be done by leaving behind uterus and the contralateral ovary. Careful selection, adequate surgical staging, careful pathologic evaluation and follow-up are important for a favorable outcome. Some of the other options include oocyte, embryo and ovarian tissue cryopreservation.

Keywords: Fertility sparing surgery, Radical trachelectomy, Gynecological cancer

Introduction
Gynecological malignancies are most often diagnosed in postmenopausal women where radical surgery is the option. These malignancies also occur in younger women in whom fertility preservation is a major issue. The incidence of cancer in younger women in reproductive age group is on the rise due to late marriage and delayed child bearing. Standard management involves removal of uterus and adnexa resulting in infertility. Fertility sparing surgery has to be considered in younger women desirous of retaining child bearing capability. There is an increased demand for fertility preservation due to increased awareness of the impact of infertility and premature ovarian failure. If the woman strongly desires to retain fertility, she needs to be counseled to weigh the benefit versus risk of persistence, progression, recurrence and metastases of the cancer. However, the surgery should be optimal without compromising gynecological safety.

Fertility sparing surgery for carcinoma of uterine cervix
Invasive carcinoma of uterine cervix is the commonest genital tract cancer in young women in developing countries because of lack of screening and preventive measures. In the developed world due to good screening programs, over all incidence of invasive cervical cancer has decreased but has a higher incidence of preinvasive and early stage cancers in young women. The incidence of carcinoma cervix in women aged between 20-49 years is reported to be 1.5 to 14.9 per 100,000.1

The standard treatment of early stage carcinoma cervix (stage I, II A) is type II or type III radical hysterectomy with pelvic and para-aortic lymph node dissection or radical radiotherapy with external beam pelvic irradiation and intra cavity radiation depending on the stage of the disease and risk factors.

A thorough evaluation is an integral part of any fertility sparing surgery. Proper and accurate staging by examination under anesthesia, if needed is done. The extent of cancer is assessed by careful review of histopathology for type and grading and by imaging techniques. Contrast MRI is as accurate as CT scan in assessing pelvic nodal disease and more accurate in assessing the extent of the parametrial disease.2 Sentinel node mapping by combining laparoscopy with lymphoscintigraphy has been shown to be more accurate. Molecular imaging using ultra small iron oxide particles to detect micro metastases has exciting possibilities in accurately staging the disease.3 Fertility sparing treatment options include excisional cone biopsy, Radical Vaginal Trachelectomy (RVT) and Radical Abdominal Trachelectomy (RAT).

Stage I A- Squamous cell carcinoma
Excisional cone biopsy- Women with stage I A, disease without lymphovascular space invasion (LVI) are candidates for treatment with cold-knife conization or laser cone biopsy alone without lymphnode evaluation. These patients have only 0.8% risk of pelvic node metastases compared to 8% with more than 3mm invasion or LVI.4

Wright et al found no significant difference in five year survival in cases of women less than 40 years with stage I A, who underwent conization versus hysterectomy. Data regarding

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LVSI is not available. Residual microinvasive carcinoma has been reported in 5% of patients with completely excised lesions. Patients with positive endocervical margins and curetttings may have a 10% chance of having a lesion >3mm (stage IA₂). These patients are not considered for cone biopsy alone. RVT is the choice for these patients. The other option may be a large cone biopsy with laparoscopic lymph node dissection as the risk of parametrial spread is very small in these patients. Large loop excision of transformation zone (LLETZ) is not advised as it is difficult to obtain 2.5 cm depth of cervical tissue and also due to difficulties in pathological assessment due to heat artifacts.

Stage IA- Adenocarcinoma

Standard treatment is hysterectomy because of its multifocal nature and also lesions may be present high up in endocervical canal. Knife cone biopsy with laparoscopic pelvic node dissection can be done provided the depth of cone is at least 25 mm and a pathology review must confirm clear margins of 5mm or more.

Radical Vaginal Trachelectomy (RVT)

It was developed by Daniel Dargent in 1987 and the results of his 28 patients was published 7 years later. Laparoscopic pelvic lymphadenectomy with or without para-aortic lymphadenectomy is performed first and then RVT is performed if nodes are negative on frozen section.

Eligibility criteria for RVT:

1. Strong desire to preserve fertility
2. Biopsy confirmed squamous cell, adenocarcinoma or adenosquamous carcinoma
3. Absence of high risk histology (Neuroendocrine tumors)
4. No Lympho Vascular Space Invasion (LVSI)
5. No evidence of lymph node metastases
6. Stage IA, with LVSI or IA₂, IB, with size of lesion less than 2 cm with limited endocervical extension as assessed by colposcopy and MRI. MRI is mandatory in all women with macroscopic tumours. The sagittal T-2 weighted images allow a clear assessment of length of endocervical canal extension into endocervix, distance between upper margin of lesion and isthmus apart from tumour size, location and parametrial spread. If the distance between upper margin of lesion to isthmus is < 1cm, the preferred treatment is neoadjuvant chemotherapy followed by RVT in patients who respond to chemotherapy.

Radical trachelectomy involves laparoscopic lymph node dissection and radical removal of cervix, upper vagina and parametrium. Cervix is amputated maintaining at least 1 cm of cervix attached to the uterus. Excised cervix is sent for frozen section, RVT is completed if there is more than 8 mm free margin. A permanent cerclage is applied on the cervix. The RVT was abandoned in 11-12% of cases due to lymph node metastases, more extensive disease than expected and inability to achieve a negative cervical margin.

Recurrence

The overall rate of cervical cancer recurrence after RVT was less than 5% and mortality was 2-3% and these results were comparable to radical hysterectomy. Most recurrences were in the parametrium or pelvic wall possibly because of insufficient parametrial excision or presence of microscopic LVSI. Size of tumour ≥2 cm, presence of LVSI, non-squamous histology are associated with a high risk of recurrence. In these patients there is a definite need for adjuvant therapy. Adjuvant radiotherapy carries high risk of premature ovarian failure and permanent loss of fertility. Neo-adjuvant chemotherapy using cisplatin, carboplatin, taxol, ifosfamide may preserve fertility. The risks of local recurrence must be weighed against the risks of adjuvant therapy.

Complications and morbidity of RVT

Perioperative complications include uterine perforation, bladder and ureteric injury, bleeding from pelvic side wall etc. Postoperative complications include cervical stenosis, hematometra, amenorrhoea, chronic white discharge, cerclage erosion, expulsion or cutting through etc.

Radical Abdominal Trachelectomy

It is the method of choice when vagina is narrow. It can be done by laparotomy or by laparoscopy, more radical excision of parametria is achieved. The technique is identical to the standard abdominal radical hysterectomy except that the upper part of uterus is preserved which is anastomosed to vagina. The disadvantages are more blood loss, cervical and isthmic stenosis and amenorrhoea which may be the result of ligation of uterine arteries.

Follow-up

There are no definite guidelines for follow-up of patients after conservative surgery. Colposscopic examination with cervical cytology with or without endocervical curettage depending on histology once in 3 months for the first 3 years, then every 6 months for 2 years. Cervical stenosis may hamper proper colposcopic examination. MRI is useful when recurrence is suspected. Hysterectomy after completion of child bearing is a matter of debate as no data are available comparing long term outcomes. It is an individualized recommendation and problems of doing it or not need to be discussed with the patient. Contraception is advised for 6-12 months. Conception can be permitted if there is no evidence of recurrence.
Pregnancy following trachelectomy

Infertility may be a problem due to cervical factor which is seen in 14-41% of patients. Cervical stenosis accounts for 40-75% of fertility issues and the reminder may be due to causes unrelated to surgery. Jolley et al in a review of 200 pregnancies following radical trachelectomy reported live birth rate of 66% with a term birth rate of 44% and preterm birth rate of 25%. No increased incidence of first trimester abortions was reported. An increased risk of second term abortions and preterm deliveries was reported. A short cervix which is less than 2.5 cm has a nine fold increased risk of second trimester miscarriage and a preterm delivery before 35 weeks of gestation. The main problem with the short cervix is cervical incompetence. Mathevet et al suggested two procedures to decrease these complications, one by placing a permanent cerclage and another by closing the cervical os in the third month of pregnancy. They reported a decrease in pregnancy losses from 50% to 22%. Other measures include prophylactic antibiotics at 14-16 weeks gestation, avoiding coitus from 20th to 36th week of gestation and steroid coverage. All these are controversial but may help in reducing prematurity and its complications. Trans Vaginal Ultrasound (TVS) monitoring for cervical length and preterm labour is a good predictor. Vaginal delivery should be avoided because a lateral cervical tear in the short scarred cervix may extend up involving uterine vessels resulting in severe bleeding. Elective cesarean section at 38 weeks is a good option.

Fertility sparing surgery in endometrial cancer

Endometrial carcinoma is the commonest genital tract malignancy in developed countries. The standard therapy for endometrial cancer includes total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para aortic node dissection depending on the risk factors and staging. 3-14% of all cases of endometrial cancer occur in younger women (<40 years of age) in whom issues of fertility preservation is important. Young patients who develop endometrial cancer often have some degree of hyperestrogenism, anovulation, obesity, lipid and carbohydrate imbalance. Nearly half of them are nulliparous with abnormal uterine bleeding. Up to 29% of premenopausal women with endometrial cancer may have a concurrent ovarian malignancy. Fertility preserving options in endometrial cancer are currently limited to hormonal methods.

Selection criteria: 
1. Stage I grade I, well differentiated tumour
2. Absence of LVSI on curettage specimen
3. No evidence of myometrial invasion on MRI
4. No evidence of metastases on imaging
5. No evidence of adnexal mass on USG/CT
6. Strong and diffuse expression of progesterone receptors on immuno histochemical studies of curettage specimen.

Patients need to be counseled about the unidentified risk of recurrence and metastases. Hormonal treatment includes progestogens, antiestrogens, GnRH agonists and aromatase inhibitors. The most widely used are progestogens which are safe and effective. Commonly used progestogen is medroxyprogesterone acetate (MPA) 400-800 mg in daily divided doses or Megesterol 160 mg daily. The levonorgestrel containing intrauterine system has been used and may be useful for maintenance therapy. Treatment is continued and endometrial sampling is done three monthly to assess the response. If disease is persistent, progressive hysterectomy is advised. In patients who respond to treatment, it is continued for another 6-9 months and patient is encouraged to conceive after that. Ramirez et al in their study of 81 patients treated conservatively with progestins found that 62 patients (76%) responded to initial hormone therapy with median time of 12 weeks. Repeat courses were given in those with partial response. Fifty two out of 81 patients responded to hormone therapy. Fifteen patients who initially responded to treatment had recurrence. Ten of the patients with recurrence were subjected to surgery and nineteen patients did not respond to hormone therapy. Twenty patients were able to conceive at least once after completing treatment. Another conservative option being tried is local excision of endometrial tissue by hysteroscope or curettage followed by adjuvant progestins based on tumour hormonal sensitivity.

Fertility conservation in ovarian tumours

Ovarian cancer is the leading cause of death from gynaecological cancers. Most of these patients are diagnosed in advanced stage and 90% are epithelial ovarian cancers. Incidence among younger women is low, in women 20-49 years it was reported as 1.6 to 16/1,00,000 and in < 20 years 0.7/1,00,000. Generally choice of treatment is debulking surgery which includes Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy (TAH with BSO), infracolic omentectomy and removal of diseased tissue as much as possible(optimal debulking) followed by chemotherapy. The treatment results in complete sterility. Conservative surgery in younger women includes ovarian cystectomy, unilateral salpingo-oophorectomy (USO), TAH and USO with preservation of contralateral ovary or BSO with preservation of uterus (these will require assisted reproduction techniques to become pregnant). Ovarian tumours which are common in young age include germ cell tumours, borderline ovarian tumours, sex cord stromal tumours and early stage epithelial ovarian tumours confined to one ovary without any extra ovarian spread.
Germ cell tumours

These are the most common ovarian cancers occurring in children and adolescents. Eighty percent of germ cell tumours are diagnosed in women who are under 30 years of age and 70-75% are diagnosed with stage-I disease. These tumours generally respond very well to chemotherapy and cure rates are high even in advanced disease. Most of these tumours exhibit tumour markers which make them amenable for easy follow-up and diagnosis of early recurrences or metastases. Zaneita et al. reported a large series of 169 young patients with malignant germ cell tumours who underwent fertility sparing surgery. They reported that conservation of uterus and the contralateral ovary was possible in 81% of patients with 5 year survival rate of 90-100%. Thirty of these women attempted pregnancy of which 28 (88%) conceived and resulted in 69% full term normal infants.

Borderline ovarian tumours (BOT)

About ten percent of epithelial ovarian tumours are BOT and occur in young women. When fertility preservation is being considered, it has to be balanced between adequate surgery to minimize recurrence and minimal surgery to optimize fertility. Marcickiewitz et al. in a series of 101 cases of BOT reported 22 women who underwent fertility sparing surgery in the form of USO in 14 patients and USO combined with cystectomy of the contralateral ovary in 8 patients. All had FIGO-stage I disease. No recurrence was seen in eight years follow-up. Nine of these women conceived, seven spontaneously, two after IVF and all delivered normal full term live babies. Fertility sparing surgery can be performed safely in early stage BOT, proper staging workup is essential.

Invasive epithelial tumours

Around 3-17% of women with ovarian cancers are < 40 years in age and most have advanced malignancy. The European Society of Gynaecology group advised that stage IA grade 1 (and probably 2) mucinous, endometroid or serous adeno carcinoma were suitable for fertility sparing surgery. Grade 1, stage I C tumours also can be considered. These patients have to be thoroughly evaluated with imaging techniques and tumour markers. Laparotomy, BSO and staging is done including pelvic and paraaortic nodal sampling. Chemotherapy with carboplatin, paclitaxel is advised if indicated. Biopsy of normal looking contralateral ovary may not be of much benefit as a focus of carcinoma may be entirely missed in a random biopsy. It is important to balance the possible risks of fertility with disease recurrence and metastases. Schider et al. reported 71 pregnancies among 48 patients who were treated conservatively and 54 of them had full term deliveries.

Other options

There will be a number of women who after undergoing fertility sparing surgery will have infertility and will require assisted reproductive techniques to achieve pregnancy. These include ovarian tissue retrieval and cryo preservation, ovarian stimulation and oocyte retrieval and/or IVF and embryo cryopreservation. Surrogacy will be required if uterus is removed to achieve pregnancy. These procedures are usually undertaken between primary surgery and the start of chemotherapy or radiotherapy.

Oocyte cryopreservation requires ovarian stimulation with the potential delay in cancer treatment and also it is contraindicated if tumour is hormone dependent. Oocyte vitrification may offer increased success rates in comparison to slow freezing. This is recommended by NICE guidelines but carries 3-5% chance of resulting in a successful pregnancy per frozen egg. Women exposed to chemotherapy drugs particularly alkylating agents have a high level of ovarian toxicity. Suppression of ovarian function through manipulation of GnRH has resulted in decreased in loss of primordial follicles and thus protection of ovarian reserve.

Reccia et al. in a study of 100 women receiving 12 months of GnRH analogs during cancer treatment found that 67% of women who were under 40 years of age had 100% return of menstrual function however, only 3 pregnancies were reported. The preimplantation genetic diagnosis may decrease the risk of disease transmission of hereditary cancers.

Conclusion

Fertility preservation in gynaecological malignancies is a rapidly evolving field which includes medical and surgical treatments to decrease the impact of cancer treatment on future fertility. A thorough counseling and a multidisciplinary approach plays an important role. Risk of cancer relapse has to be weighed against fertility preservation. Appropriate patient selection, careful oncological reproductive and obstetric counseling is very important. Pregnancy appears safe after cancer treatment but depends on individual patient characteristics.

References


