Fertility preservation in cancers

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Recommendations of fertility sparing surgery or medical management

Desire of patient or her parents to retain fertility potential if possible

Optimal cancer therapy should always supersede fertility preservation as a primary objective

Why fertility preservation?

With recent advances in oncology, cancer survival rates are increasing, therefore, issues affecting long term cancer survivors have become more important and widely recognized. The ability of having genetically related children is an important issue for patients surviving cancer

Cancers under consideration

- Cervical cancer
- Endometrial cancer
- Ovarian cancer

Cervical cancer

- 43% women are diagnosed for cervical cancer in their child bearing age
- 46%of cervical cancers present with stage 1 disease, usually curable by radiation/surgery.
- Squamous cell carcinoma more common than adeno carcinoma. However, this trend appears to be changing towards an increase in incidence of adenocarcinoma.

Definitive conservative therapy for cervical cancers

Cone biopsy

- Squamous cell carcinoma in situ
- FIGO stage $1A_1$ microinvasive squamous cell cervical lesion (microscopic lesions with stromal invasion less than 3 mm depth and less than 7 mm wide)

Cone biopsy as definitive therapy

- Excisional cone biopsy with negative margins with stage $1A_1$ lesions
- Positive margins may have a 10% chance of having lesion >3mm stage $1A_2$ and not candidates for cone biopsy
- 0.8% risk for pelvic node metastasis, compared with 8% with >3 mm stromal invasion.
- Rate of fertility not compromised though risk of spontaneous second trimester loss and premature delivery is higher.

Definitive conservative therapy for cervical cancers contd….

Fertility sparing radical surgery: Radical vaginal trachelectomy and pelvic lymph-adenectomy

- FIGO stage $1A_2$ to 1B invasive squamous cell carcinoma or adenocarcinoma
- Adenocarcinoma in situ (AIS) and microinvasive adeno-carcinoma

Eligibility criteria for radical vaginal trachelectomy

- Biopsy confirmed cervical squamous cell carcinoma, adenocarcinoma, adeno-squamous carcinoma
- Desire to preserve fertility
- FIGO $1A_1$ with lymph vascular space invasion, $1A_2$, $1B_1$ with no lymph node metastasis
- Lesion size <2cm or, <3cm if exophytic
- No evidence of distant metastasis on preoperative imaging and adequate cervical length $\geq$ 2 cm
- Limited endocervical involvement on colposcopy
- MRI to assess extent of tumour

Complication of radical vaginal tracheletomy

- 17% 1st trimester and 12.5% 2nd trimester loses (lack of cervical mucus, cervical incompetence, and sub-clinical chorioamnionitis)
- Rates of pre-term delivery 50%
- Cervical stenosis with hematometra reported occasionally

Ovarian cancer

- Germ cell tumor: unilateral salpingo-oopherectomy (ULSO) with omentectomy, peritoneal washings, biopsies and pelvic & para-aortic lymph node sampling as staging procedure.
- Sex cord stromal tumors: ULSO followed by platinum based chemotherapy
- Epithelial ovarian tumors with low malignant potential (serous and mucinous): ULSO or cystectomy with the same staging procedure. Recurrence rate 12%-15% & spontaneous pregnancies in 50%. ***Seracchioli et al., 2001 Fertil Steril***
- Invasive epithelial tumors: 7-8% in women under 35 years; stage 1 only fertility preservation with ULSO and staging procedure; 3 monthly follow up-USG & CA125

Effect of radiation on ovary & uterus

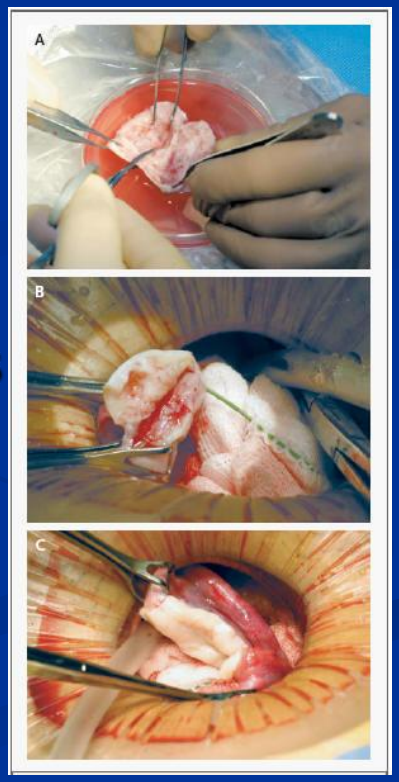
- Age: POF with low dose; total depletion of follicular pool at higher dose
- Dose:
  - women > 40 years: 5-6Gy total POF
  - Women<40 years: 20 Gy total POF
  - Women <35 years tend to resume normal menses
- Type: TBI for stem cell transplantation causes 90% gonadal failure
- Long term sequelae: no increase in teratogenicity
- Infertility:
  - pregnancy loss 38% vs12%; preterm labour 62% vs 9%;
  - growth retardation62% vs 6%

Effect of chemotherapy on ovary & uterus

- **Duration and dose**: toxicity through impairment of follicular maturation/depletion of primordial follicles
- **Age:** rate of amenorrhea 35-40% in women <40 years
  80-95% in >40 years
- **Type of chemotherapy:** Act on resting primordial follicles. Recovery of ovarian function rare with busulphan and cyclo-phosphamide. Melphalan shows less reproductive toxicity
- **Long term sequelae:** No toxicity to off spring if used before pregnancy. 6 months recommended between completion of chemotherapy and pregnancy for prevention of teratogenicity.

How to reduce cyto-toxic effect of radiation and chemotherapy

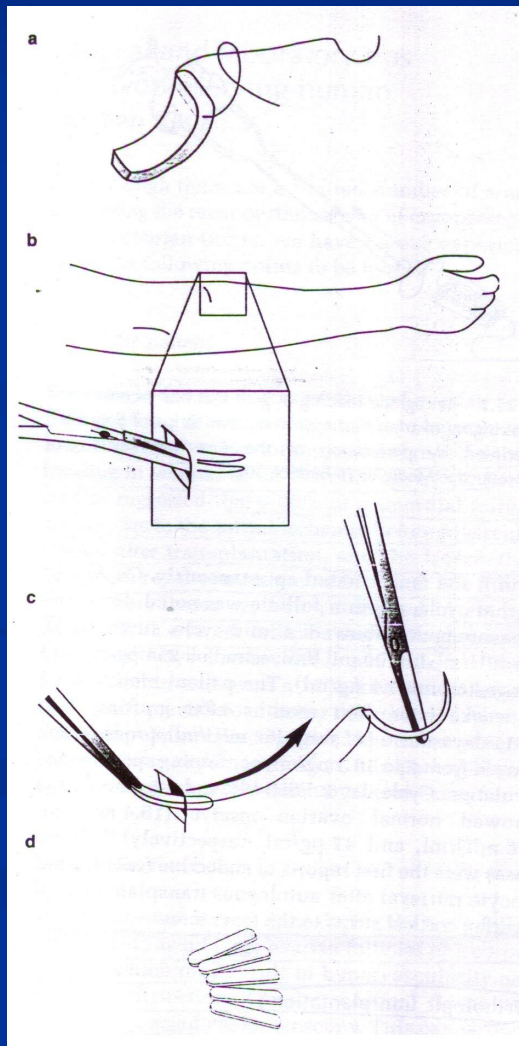
- GnRH agonist may render the germinal epithelium quiescent by creating an artificial pre-puberscent state.
- OCP to suppress ovaries
- IVF with frozen embryos
- Oocyte freezing
- Cryopreservation of ovarian cortical strips
  - Autologous orthotopic transplantation
  - Hetrotopic xenograft transplantation
- Ovarian transposition



Transplantation of ovarian tissue into recipient medulla

Ovarian transposition

- Procedure where ovaries with their attached blood supply are surgically detached from uterus and transposed to an area outside the planned radiation field.
- Radiation is reduced to 10 % of the dose and preserves ovarian function for future fertility.
- High risk of premature menopause with fertility preservation only in 15%
- Risk of occult metastasis is there.



Endometrial carcinoma

Pre treatment evaluation of patients considering conservative therapy

- History and physical examination
- Hysteroscopy and curettage
- USG and CA 125 for ovarian assessment
- MRI

Atypical hyperplasia

- High dose continuous progestin therapy: 80mg MPA daily or 40 to 160mg magesterol acetate daily for 6 months
- GnRHa good regression in hyperplasia without atypia
- GnRHa with high dose progestogens
- Danazol (400mg) and Tamoxifen 20mg daily
- D-IUD
- Insulin sensitizing agents (metformin) as adjunct to progestogen

No standard conservative therapy has been universally accepted. Various trials have been reported by different groups only for stage 1a & b with endometrial sampling every 4 weeks during treatment and in follow-up period

- Imai *et al.*, ***Eur J Gynecol Oncol 2001:*** 15 patients: 47 persistent cancer, 50% recurred after discontinuation of treatment. 2 out of remaining 6 conceived with ART
- Randall *et al.*, ***Obstet Gynecol 1997:*** out of 25 women 5 delivered
- Kim *et al.*, ***Cancer 1997***: 6 viable infants delivered
- Plante et al., ***Curr opin Oncol 2000*** : 20 successful pregnancies after pharmacological reversal of disease

Medical management of endometrial cancer

- ***MPA***: 200-800mg daily for 18-37 months recurrence in 40 months
- ***Magesterol acetate:*** 160 mg daily for 3-23 months recurrence in 19 to 44 months
- ***Norethisterone acetate:*** 30mg daily for 6 months recurrence not reported
- ***Hydroxy progesterone caproate:*** 2 to 3 gm daily for 3 -6 months recurrence not reported

Key points

- Squamous cell Ca in situ & FIGO stage1 a1: cone biopsy (Variable results with adeno-carcinoma)
- Invasive squamous cell Ca stage 1a2 to 1b: radical trachelectomy with lymphadenectomy
- Germ cell tumors, low malignant potential and early invasive epithelial tumors: ULSO with complete staging procedure.
- Endometrial hyperplasia with atypia and stage 1 grade I to 2: high dose progestogens, GnRHa, tamoxiphen, danazol and insulin sensitizers.

Key points contd

- Effect of radiation and chemotherapy on ovary may be progressive and irreversible, resulting in amenorrhea and infertility
- Damage to gonads can be minimized by use of GnRHa, OCP, IVF, cryopreservation of oocytes & ovarian cortical tissue and transposition of ovaries.
- The desire on part of patient to preserve fertility is essential but optimal cancer therapy should always precede as primary objective.
- Need for hysterectomy after child bearing and oophorectomy at the time of hysterectomy are options which are unresolved and need to be addressed.

Thank you