

**Fertility Preservation in
Women with Cancer**

Leslie R. DeMars
Dartmouth-Hitchcock Medical Center



Objectives

The audience will understand:

- How cancer therapy affects fertility.
- Who should be considered for fertility preservation.
- What fertility conserving options exist for women with gyn cancers.

Patient #1

- 28 year old WF with 7 cm cystic and solid right ovarian mass
- To OR for oophorectomy:
 - Pathology is grade 3 clear cell cancer
- What is the most appropriate management of this woman?

Patient #2

- 21 yo G0 with 3 cm cervical lesion
- Biopsy showed rhabdomyosarcoma
- Initial recommendation for radical hysterectomy
- Presented to DHMC for second opinion

Patient #3

- 35 year old G0 with 2cm small cell cancer of the cervix.
- Imaging shows disease confined to cervix

Fertility Preservation

- Each case should have consideration for fertility preservation:
 - Each seeking future pregnancy
 - Age suggests potential for fertility
 - Each with Stage I cancer
 - None require radiotherapy as primary treatment

Pre-menopausal cancer

- 113 per 100,000 women have pre-menopausal cancer
- Children/adolescents: leukemia, lymphoma, germ cell tumors of ovary
- Young women: Lymphoma, germ cell tumors, breast cancer, cervical cancer, epithelial ovarian cancer

Importance?

- Cancer patients were told of the importance of cure over cost (their fertility), and pregnancy was discouraged.
- Cancer patients who receive timely consultation from reproductive subspecialists are more satisfied with their cancer care and have a better quality of life than women with whom fertility was not discussed.
- Childhood cancer survivors have 8% infertility rate vs 0.8% rate of siblings.

Pregnancy after cancer therapy

- Appears to be safe, with PTL being slightly more frequent.
- No increased risk of chromosomal abnormalities
- Often delayed for > 2 years after therapy, no data to support need for delay

Patient #1

- 28 year old WF with 7 cm cystic and solid right ovarian mass
 - Pathology is grade 3 clear cell cancer
 - Contralateral ovary appears normal, no obvious extra-ovarian disease
- **PRE-OPERATIVE PLANNING INCLUDED CONSERVATIVE SURGERY IF POSSIBLE.**
- RSO, staging biopsies confirmed Stage I disease
- Post-op chemotherapy needed

Chemotherapy induced ovarian failure

- Phenomenon most often seen with alkylating agents such as cyclophosphamide, busulfan, chlorambucil
- Not limited to cancer patients.
- Cytotoxics affect dividing cells: granulosa cells vs oocytes
 - Ovaries s/p chemo have ↓primordial follicles but ↓↓ maturing follicles
- Dose and age dependent
 - POF age 20 9.5 gms of cyclophosphamide
 - POF age 40 5.2 gms of cyclophosphamide

Oocytes and ovaries

- Germ cells to oocyte
 - In utero 7,000,000 germ cells
 - 15 weeks 1st meiotic division – oocytes
 - 20 weeks oocytes surrounded by granulosa cell layer becoming primordial follicle
 - At birth 1,000,000 follicles
 - At puberty 300,000
 - At menopause 1,000
- Follicular growth in fetus independent of gonadotropins, continues through prepuberty
- Follicular development at puberty requires FSH acting on granulosa cells and LH response

Oocytes and follicles

- As soon as primordial follicles are formed, atresia begins.
- Apoptosis seems to be major mechanism
 - Oocyte apoptosis in fetus
 - Granulosa cell apoptosis in adult

Chemotherapy and ovarian function

- Pre-pubertal ovaries should be resistant:
 - No granulosa cell activity, oocytes are in arrest
- Pubertal ovary: FSH, E2, LH responsiveness
- Peri-menopausal ovary: inhibin B and AMH levels fall as follicle number decreases, FSH rises, E2 nl
- Mechanism of ovarian damage uncertain
 - See normal or decreased follicle counts
 - Granulosa cells should be more sensitive than oocyte

Patient #1's options

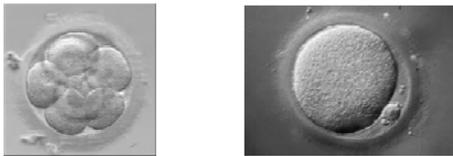
- Embryo cryopreservation
- Ovarian cryopreservation
- Oocyte cryopreservation
- Gonadal suppression
 - GnRH agonist use controversial
 - Primordial follicles have no FSH or GnRH receptors
 - GnRH use increased spontaneous menstruation (OR 3.46) and spontaneous ovulation (OR 5.7) compared to controls, but no difference in spontaneous pregnancy

Cytotoxins and ovarian failure

- High risk: cyclophosphamide, chlorambucil, melphalan, busulfan, nitrogen mustard, procarbazine
- Intermediate risk: *cisplatin*, adriamycin, *taxanes*
- Low risk: methotrexate, 5-fluorouracil, vincristine, bleomycin, actinomycin D

Embryo cryopreservation

- Proven technique when risk of permanent ovarian failure is high
- 3 weeks for ovulation induction and retrieval
- Relative contraindication for ER+ cancer
- Religious and ethical constraints

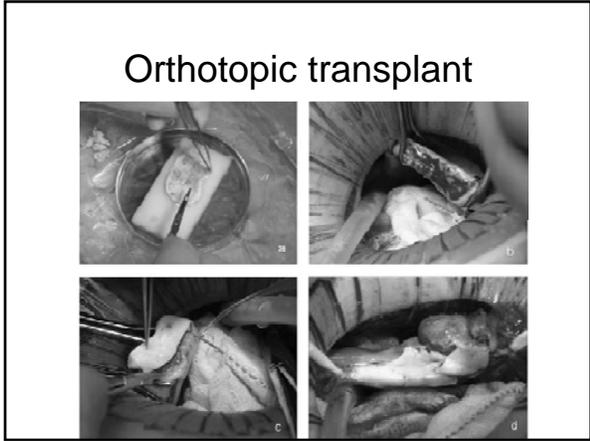


Oocyte cryopreservation

- Still considered experimental
- Oocytes more sensitive to cryoinjury than embryos
 - Immature oocytes freeze better than mature oocytes, but have lower pregnancy rates
 - 3 week time constraint for mature oocytes
- Best results to date using vitrification
 - Fertilization rate 70.6%
 - Live birth rate per oocyte 4.5%
 - Live birth rate per embryo transfer 29.4%

Ovarian tissue cryopreservation

- Orthotopic or heterotopic transplantation done
- Case reports of pregnancy
- High attrition rate with failure of grafts to revascularize



Patient #1

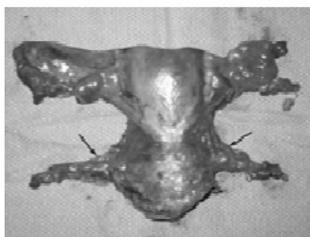
- Favorable age and cytotoxics allowed for conservative management
- Menses continued through chemotherapy
- Spontaneous pregnancy with full term delivery 5 years after completing chemotherapy
- One subsequent miscarriage
- If chemo not going to be ablative, no indication for suppression of function,

Patient #2

- 21 year old G0 with rhabdomyosarcoma
- Imaging confirmed cancer confined to cervix.
- Stage I rhabdomyosarcoma treated with surgery and chemotherapy
- Both surgery and chemotherapy require consideration of fertility conservation
- **LESS IS MORE**

Surgery for cervical cancer

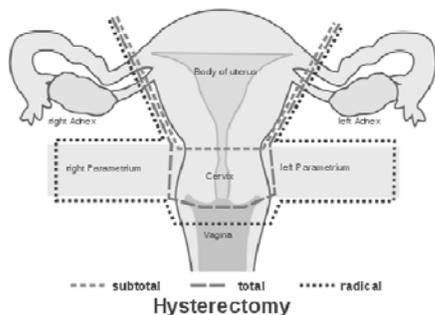
- CKC/ultraconservative
- Trachelectomy
- Hysterectomy
- Radical hysterectomy
- Radical trachelectomy



Radical trachelectomy

- Abdominal, vaginal and robotic approaches
 - 5% intra-op; 20% post-op complications
- 500 VRT reported: recurrence rate < 5%
- Radical vaginal trachelectomy with > 200 successful pregnancies
 - PTL 25%
 - Abdominal cerclage
- Pregnancy not impaired despite lacking cervix

Radical hysterectomy vs. Radical trachelectomy



Trachelectomy

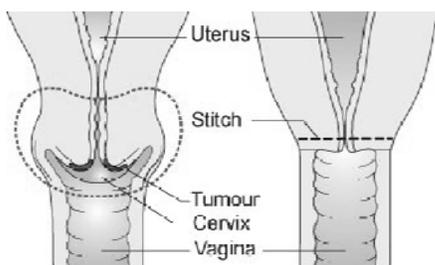


Diagram showing the parts removed with a trachelectomy surgery
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Rhabdomyosarcoma of cervix

- Abdominal trachelectomy with cerclage placement
- 12 months of VAC chemotherapy
- Unmarried college student
 - Ovarian suppression
 - Oocyte cryopreservation
 - Embryo cryopreservation with donor sperm
 - Ovarian transplantation

Cytotoxins and ovarian failure

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Patient #2

- Risk of permanent amenorrhea with VAC given her age < 10%.
- No suppression
- Spiritual opposition to ART
- Cessation of menses during chemotherapy with resumption < 1 year later
- Spontaneous pregnancy and term Cesarean delivery

Patient #3

- 35 year of WF with 2 cm small cell cancer of the cervix
- Small cell cancer poor histology
- Fertility conservation discussed at initial visit; **RAPID CONSULTATION WITH REI OBTAINED TO ASSIST TREATMENT PLANNING.**
- Tumor board presentation to suggest best cancer treatment

Patient #3

- Treatment plan: simple trachelectomy followed by etoposide and cisplatin chemotherapy
- REI plan: during recovery from trachelectomy, superovulation, oocyte retrieval and embryo cryopreservation
- Trachelectomy without complication
- Evaluation for IVF cycle -- azospermia

Further considerations

- Endometrial cancer and complex hyperplasia with atypia
 - Progestin therapy
 - Recurrence risk
 - REI consultation for ovulation induction
- Low malignant potential tumor of the ovary
 - Surgical therapy to remove all gross visible tumor
 - Recurrence risk
 - Careful surveillance with REI consultation
- Consider definitive surgery when childbearing complete

Take home points

- Fertility preservation should be a part of initial evaluation
- Multi-disciplinary approach
- Most gyn cancers will tolerate a 2-3 week delay in initiation of therapy (not GTN)
- Less is more
