

FERTILITY PRESERVING OPTIONS FOR EARLY STAGE CERVICAL CANCER

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Disclosure

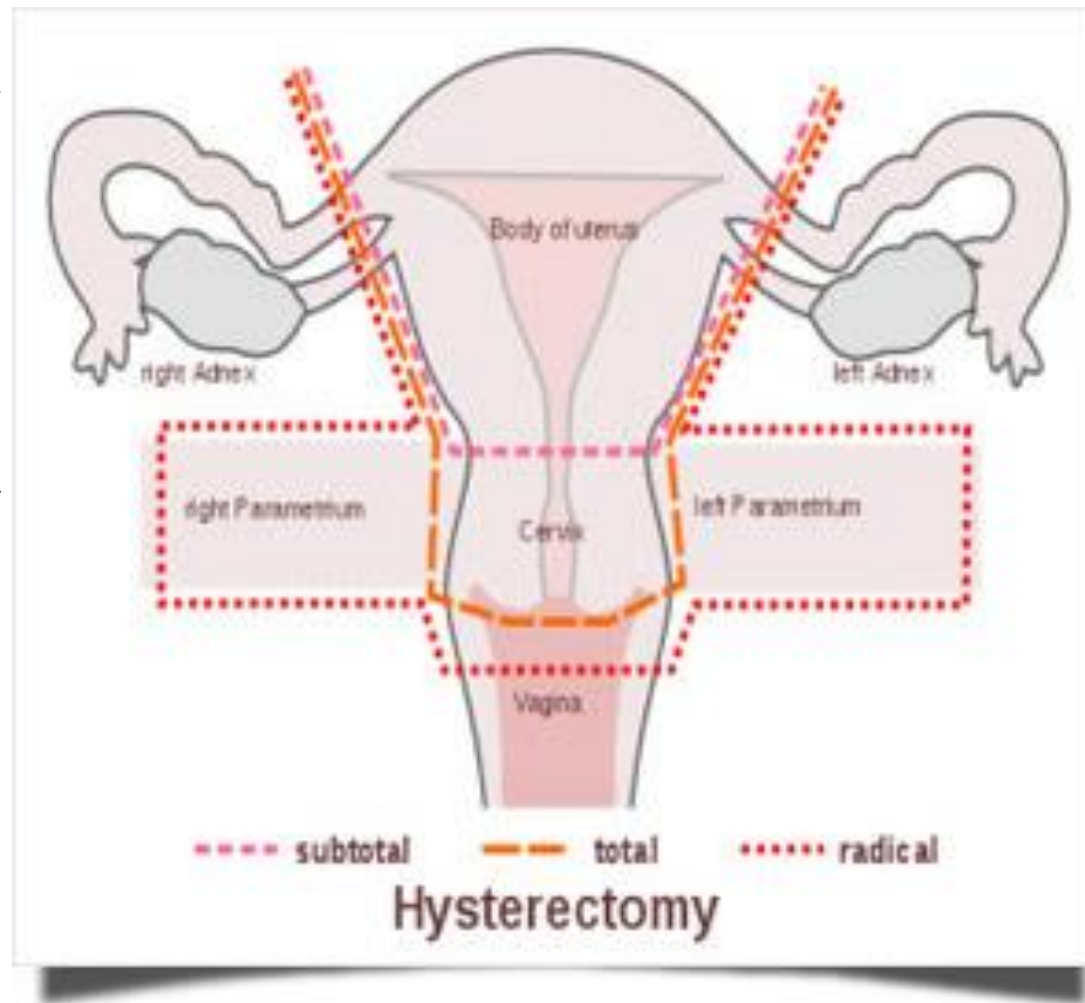
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Cervical Cancer

- 2012 estimated new cases for cervical cancer in the US: 12,170
- 2012 estimated deaths: 4,220
- USA: 5-year survival for localized disease in Caucasian women under 50 yrs of age was 94.2%
- SEER data reports that 42% of cervical cancer patients will be diagnosed at <45 yrs of age
- Forty-eight percent of women with early stage cervical cancer may qualify for fertility preserving treatment

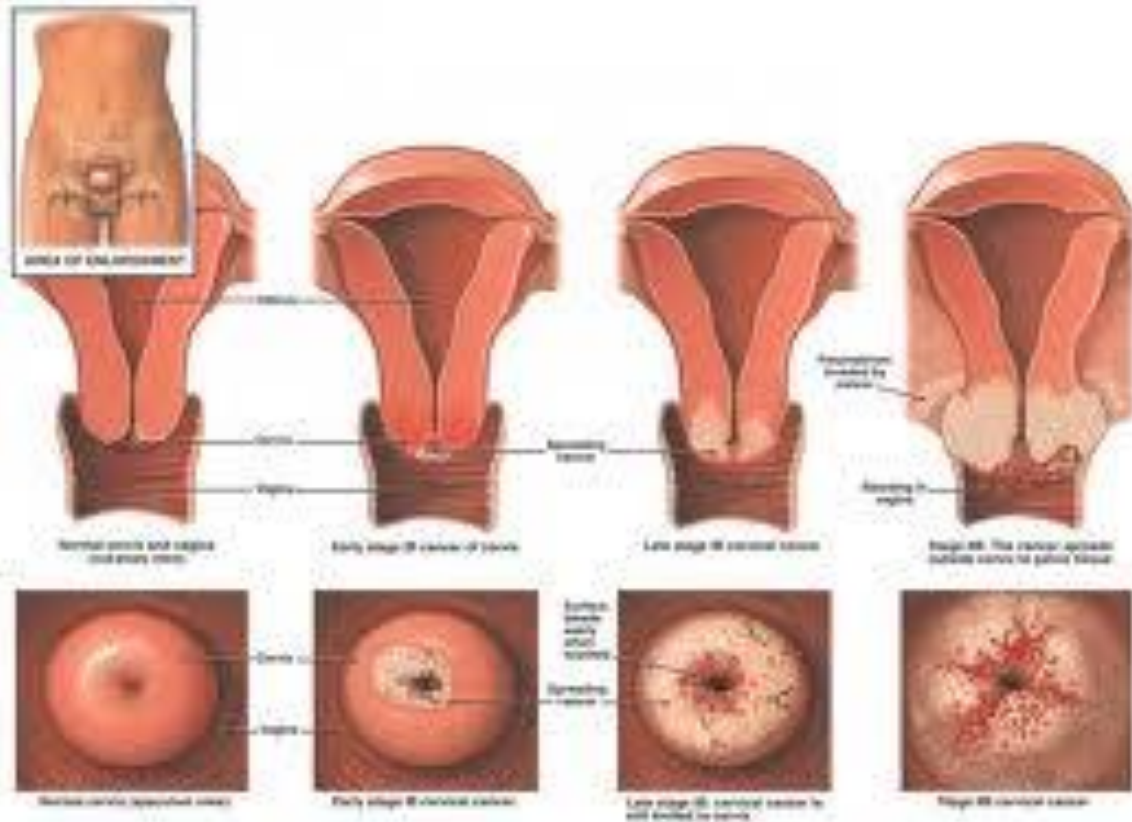
Early Stage Cervical Cancer

- Standard treatment for early stage cervical cancer
 - ▣ Simple hysterectomy
 - ▣ Radical hysterectomy and pelvic lymph node dissection
- Fertility-preserving surgery for early stage cervical cancer
 - ▣ Cervical conization
 - ▣ Radical trachelectomy and laparoscopic lymphadenectomy



Early Stage Cervical Cancer

- Early Stage Cervical Cancer is confined to the cervix
- Stage Ia cervical carcinoma – Preclinical invasive carcinoma that can be diagnosed only by a microscope
- Stage Ib cervical carcinoma – A clinically visible abnormal cells that is confined to the cervix of the uterus
- Stage Ib1 – Primary tumor not greater than 4.0 cm in diameter.



Simple hysterectomy or Radical hysterectomy and pelvic lymph node dissection
 Cervical conization
 Radical trachelectomy and laparoscopic lymphadenectomy

Advanced Stages of Cervical Cancer

- Stage Ib2 – Primary tumor is greater than 4.0 cm in diameter.
- Stage IIa cervical carcinoma – Extension into the upper vagina
- Stage IIb cervical carcinoma – Extension into the parametrium
- Stage IIIa cervical carcinoma – Extension into the lower vagina
- Stage IIIb cervical carcinoma – Extension into the pelvic sidewall
- Stage IVa cervical carcinoma – Extension of the tumor into the mucosa of the bladder or rectum
- Stage IVb cervical carcinoma

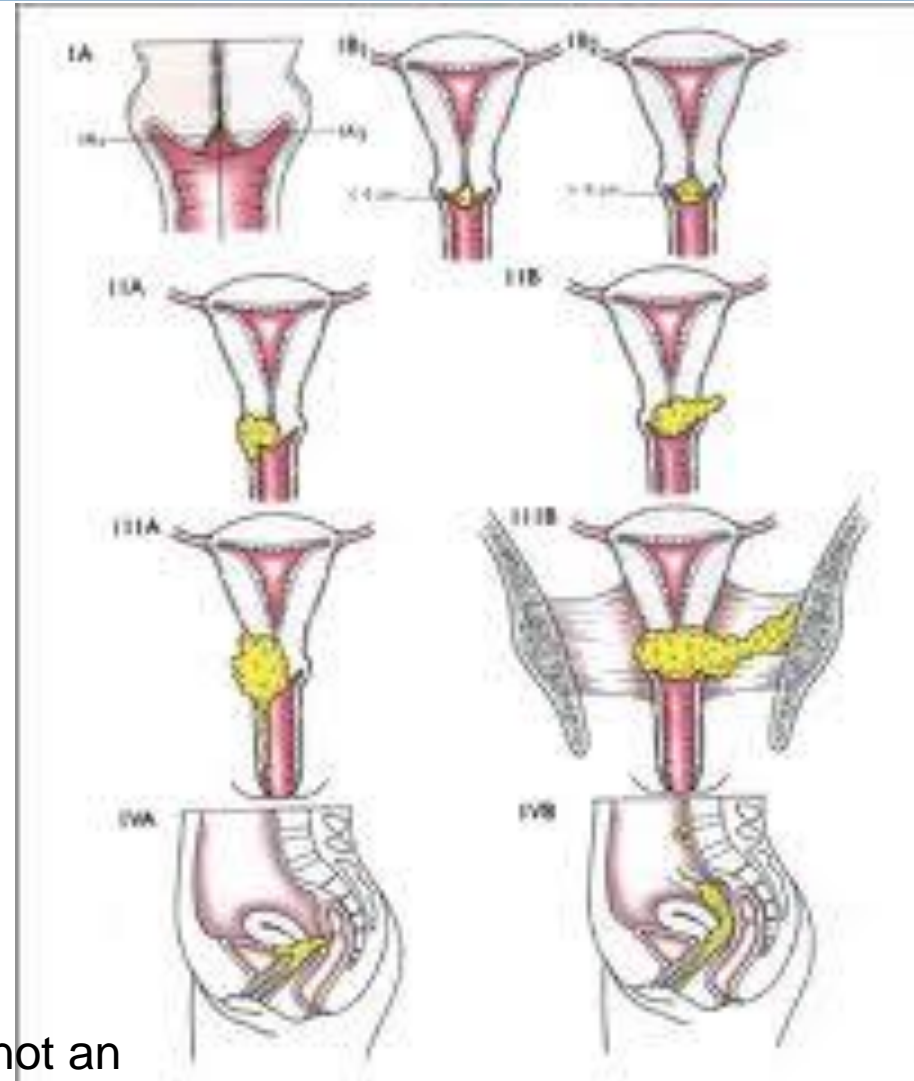


Figure 1. Staging of uterine cervix carcinoma according to FIGO[®].

Surgical fertility preserving treatments not an option

Fertility Preserving Treatment: Conization

- Stage IA1: Conization
 - ▣ Stage IA1 without lymphovascular space involvement, negative margins and normal endocervical curettage
 - ▣ Risk of lymph node metastasis <1%
 - ▣ 5 yr survival 98%-100%
 - ▣ Recurrence rate of 3%
- Complications from cone knife conization
 - ▣ Increased preterm delivery: RR: 2.59 (95%CI: 1.8-3.72); RR: 2.78 (95% CI: 1.72-4.51)
 - ▣ low birth babies: RR: 2.53 (95%CI: 1.19-5.36); RR: 2.86 (95%CI: 1.37-5.97)
- Close follow-up after pregnancy is needed

Fertility Preserving Treatment: Radical Trachelectomy

- Stage IA2-IB: Radical Trachelectomy
 - ▣ Stage IA1 with lymphovascular space invasion, stage IA2, or stage IB1
 - ▣ Tumor size ≤ 2 cm and stromal invasion less than 1.0 cm
 - ▣ Tumor limited to the cervix
 - ▣ Lymph node dissection should be performed prior to trachelectomy
 - ▣ No evidence of pelvic lymph node metastasis and/or other distant metastasis
 - ▣ Risk of lymph node metastasis $< 1\%$
 - ▣ Alexander-Sefre et al found no significant difference in 5 yr overall survival rate and 5 yr progression-free rate between radical trachelectomy and radical hysterectomy
 - ▣ 5 yr survival 98%-100%
 - ▣ Recurrence rate of 3-4%; low death rates: $< 3\%$

Fertility Preserving Treatment: Radical Trachelectomy

- Complications from radical trachelectomy
 - ▣ 1 cm cervical stoma is necessary to reduce risk of preterm delivery.
 - ▣ No significant difference between intraoperative and postoperative complications between RT and RH
 - ▣ Injury to the ureter, bladder and rectum
 - ▣ Painful menses, abnormal paps, irregular bleeding, excessive vaginal discharge, problems with the cerclage suture, stenosis, no menses and sexual inactivity
- Close follow-up after pregnancy is needed

Types of Radical Trachelectomy

- Vaginal Radical Trachelectomy
 - Low rates of recurrence 2.7%-4.3%
 - Vaginal approach, no abdominal incisions, however surgery is challenging
- Abdominal Radical Trachelectomy
 - Low intraoperative complications and recurrence rate 3%
 - Can be performed on patients with distorted cervico-vaginal anatomy, better resection of the margins, easier to do in nulliparous patients
 - Longer hospital stay, more blood loss and wound complications
- Laparoscopic Radical Trachelectomy
 - Has all the advantages of ART but with less invasive surgery
 - Safe, largest series of 32 patients reported one recurrence
- Robotic Radical Trachelectomy
 - Appears safe, number of studies limited
 - Advantages: better motion with finer instruments, precision, and 3-D image. Maintain better blood flow to the uterus, less blood loss and decreased hospital stay

Oncological Outcomes in Patients with Early Stage Cervical Cancer who underwent Trachelectomy

Types of Trachelectomy	# of patients	Recurrence (n)	Deaths (n)
Vaginal Trachelectomy 10 studies	845	35	20
Abdominal Trachelectomy 10 studies	244	7	0
Laparoscopic Trachelectomy 7 studies	57	2	2
Robotic Trachelectomy 6 studies	25	0	0

Follow-up After Radical Trachelectomy

- Patients should be seen every 3-4 months for the first 2 yrs, then every 6 months and annually after the 1st 5 yrs
- Follow-up entails cytology and colposcopy in every visit
- Cytology is a problem with 58%-60% of pap tests having atypical cells with no true disease found
- MRI can be done at 6, 12, and 18 months
 - ▣ Findings can be difficult due to the distorted anatomy

Risk Factors Associated with Recurrence: Need for Postoperative Treatment

- High risk factors
 - ▣ Positive or close resection margins
 - ▣ Positive lymph nodes
 - ▣ Parametrial involvement
 - ▣ Radiation and chemotherapy is needed
- Intermediate risk factors
 - ▣ Deep stromal invasion
 - ▣ Large tumor size
 - ▣ Lymphovascular invasion
 - ▣ Radiation should be given to decrease recurrence
- Ovarian Transposition
 - ▣ 90% ovarian function after vaginal brachytherapy and 60% in patient undergoing pelvic radiation
 - ▣ Preserves ovarian function to prevent premature menopause
 - ▣ Complications: chronic ovarian pain and ovarian cysts

Neoadjuvant Chemotherapy and Conservative Surgery

- Neoadjuvant chemotherapy can be given prior to conservative surgery
- Very small studies examining outcome of using neoadjuvant chemotherapy
 - ▣ Rob et al. 9 patients received 3 cycles of cisplatin-based chemotherapy regimen; conization or simple trachelectomy with PLND; no recurrences
 - ▣ Maneo et al. 21 patients with larger tumors <3 cm, stage IB1 received 3 cycles of chemotherapy followed by conization and PLND; no recurrence

Summary

- Conization, Simple and Radical Trachelectomy are safe, fertility preserving procedures in selected patients
- All types of radical trachelectomy are safe and result in similar recurrence rates as radical hysterectomy
- Pelvic lymph node dissection is necessary prior to performing the trachelectomy and the nodes must be negative
- Neoadjuvant chemotherapy prior to conservative surgical treatment may be in option in selected patients

FERTILITY AFTER CERVICAL CANCER AND FERTILITY PRESERVATION OPTIONS

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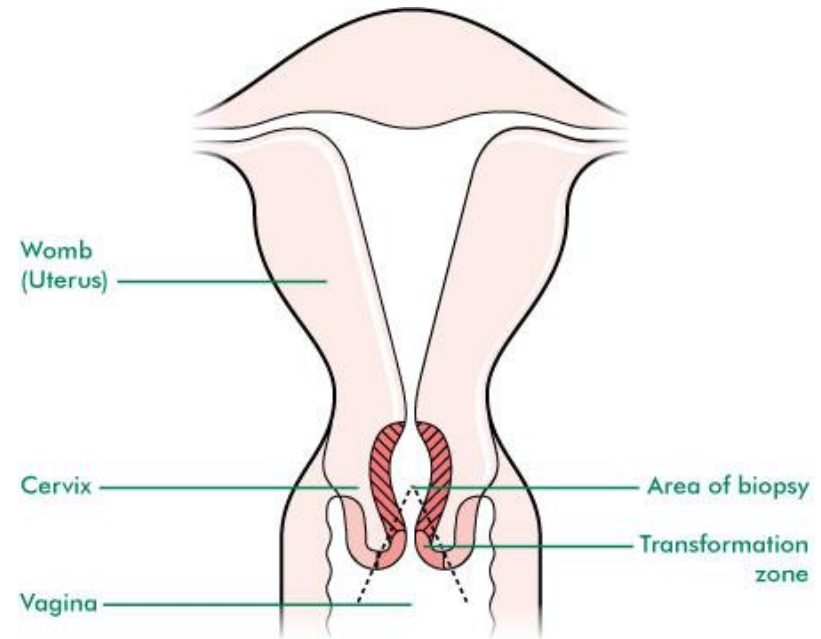
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Fertility after cervical cancer surgery

- Scope of surgery
 - ▣ **Cone biopsy, LEEP**
 - Should have minimal impact on fertility unless complicated by uterine scarring or cervical stenosis, intrauterine insemination may help
 - Risk of preterm delivery (depth of cone, number of surgeries)



Simoens et al, BJOG, 2012
Kim et al, Gynecol Oncol, 2012
Mangler et al, J Perinat Med, 2012
Speiser et al, Int J Gynecol Cancer, 2011

Fertility after cervical cancer surgery

▣ Trachelectomy

- Unclear fertility impact
 - One small study: 66% of women achieved pregnancy in 6 months
 - Probably does impact fertility however
- Risk of preterm delivery
 - Up to 50% may deliver preterm

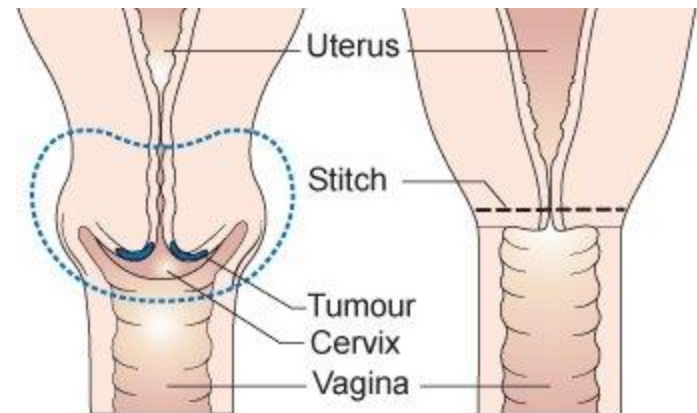
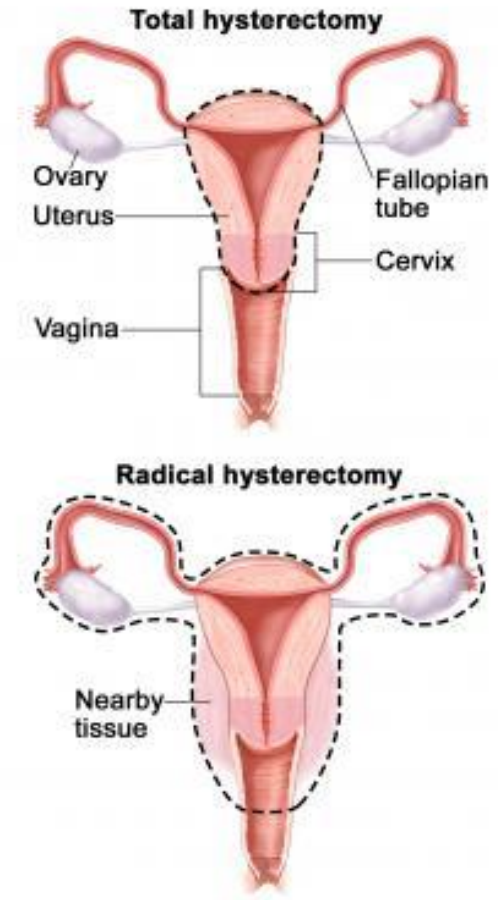


Diagram showing the parts removed with a trachelectomy surgery
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Simoens et al, BJOG, 2012
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Fertility after cervical cancer surgery

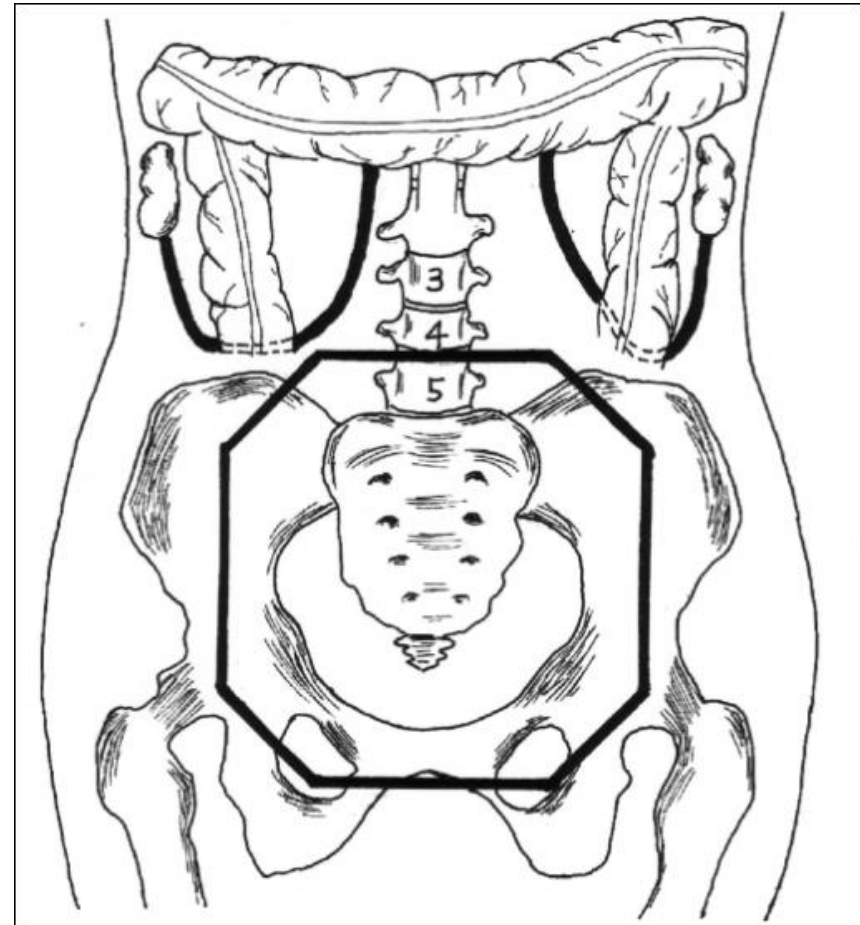
- Scope of surgery
 - ▣ **Radial hysterectomy without removing ovaries**
 - Should have normal ovarian function if no chemo/radiation afterwards but can be diminished
 - Removing one ovary may increase risk of early menopause
 - Option to use a gestational carrier
 - ▣ **Radical hysterectomy with removing ovaries or after chemo/radiation**
 - Option to use an egg donor with a gestational carrier



Fertility after cervical cancer surgery

▣ transposition of the ovaries

- Difficult to access ovaries to retrieve eggs, ovaries function less well, increased risk for early menopause
- best option is using an egg donor with a gestational carrier



Impact of radiation treatment

- Doses of $<2\text{Gy}$ will kill $\sim 50\%$ of the eggs
 - ▣ Cycles resume but at risk for early menopause
- Depends on age and dose, typical dose for whole pelvis external beam radiation is $\sim 40\text{ Gy}$
 - ▣ In young women, $10\text{-}20\text{Gy}$ may induced premature menopause
 - ▣ In older reproductive age women >40 , only 6 Gy may induce premature menopause
 - ▣ Risk of ovarian failure is almost certain after radiation

Impact of chemotherapy

- Depends on age and dose
- Alkylating agents are the most damaging
- Cisplatin and 5-FU are less damaging but can still significantly lower egg count

- **Best option: preserve eggs/embryos before exposure to chemo and radiation**

Fertility preservation options

- **Egg or embryo freezing** prior to chemo/radiation
 - ▣ Takes 2-4 weeks (may delay treatment)
 - ▣ Expensive: egg freezing ~\$6,000, embryo freezing ~\$13,000
 - ▣ FSH injections given for 10 days to stimulate egg production by ovaries
 - ▣ Egg retrieval performed (transvaginal ultrasound guided needle under anesthesia)
 - ▣ Eggs either frozen or fertilized with sperm and then frozen

Fertility preservation options

- **Ovarian tissue or whole ovary freezing**
 - Tissue can be reimplanted later, some patients may resume ovulating
 - Highly experimental, not widely available
 - Not effective/warranted if patient had radiation treatment or hysterectomy

Fertility preservation options

LupronDepot[®]
(leuprolide acetate for depot suspension)

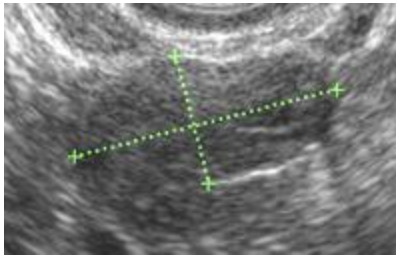
- **Depo Lupron treatment**
 - ▣ Lupron treatment during chemotherapy may partially protect ovaries from chemotherapy (controversial)
 - ▣ Not as effective as egg/embryo freezing before treatment
 - ▣ Not effective with radiation treatment

Evaluating a patient for fertility

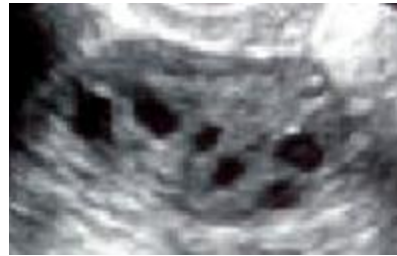
- What factors are involved?
 - Hysterectomy?
 - Exposure to radiation/chemo?
 - Other infertility issues (sperm, fallopian tubes, age)
- Assessing ovarian reserve
- Patient's comfort level with third party reproduction
 - Gestational carrier ("surrogate")
 - Egg donor (known or anonymous)

Ovarian reserve testing

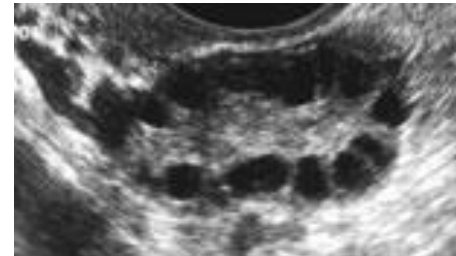
- Blood tests: FSH, estradiol, AMH
- Ultrasound: antral follicle count



Low



Normal



High

Success rates with frozen embryos

Thawed Embryos From Non-Donor Oocytes

	<35	35-37	38-40	41-42	>42
Number of Transfers	11858	5865	4411	1521	1088
Percentage of transfers resulting in live births	38.7	35.1	28.5	21.4	15.3
Average number of embryos transferred	1.9	1.9	2.1	2.2	2.1
Percentage of live births with twins	32.4	27.2	22.1	16.9	9.6
Percentage of live births with triplets or more	1.5	1.5	1.1	1.1	0.9

- Age is the most important indicator of success with IVF

Success rates with frozen eggs

- Harder to predict
- Egg freezing is still relatively new compared to embryo freezing
- Depends on age, number of eggs collected, fertilization rate, quality of embryos
- Allow for woman without a partner yet to preserve fertility without committing to the use of donor sperm

Success rates with egg donation

Donor Oocytes (all ages)

	Thawed Embryos	Fresh Embryos
Number of Transfers	6183	9321
Percentage of transfers resulting in live births	34.8	55.6
Average number of embryos transferred	2.0	1.9

- The patient's age no longer affects success rates
- Most center's require the patient to be <50 yo

Success rates with gestational carriers

	<35	35-37	38-40	41-42	>42
Number of cycles	300	184	231	101	43
Percentage of cycles resulting in pregnancies	55.3	46.2	39.4	28.7	20.9
Percentage of cycles resulting in live births	48.7	38.0	29.9	16.8	4.7

- Probability of pregnancy is determined by age of genetic mother (intended parent)
- Requires legal consultation, check state laws
- Preferable to use compassionate/known gestational carrier when possible

Additional resources

- IVF success rates, or to find a clinic near you:
 - www.cdc.gov/art
 - www.sart.org
- Fertility after cancer and preservation information:
 - www.fertilehope.org
 - www.resolve.org
 - <http://oncofertility.northwestern.edu/patients>