FERTILITY PRESERVING OPTIONS FOR
EARLY STAGE CERVICAL CANCER

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Disclosure

- I have no relationships or financial compensation from any drug companies or industries
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

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%
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

<table>
<thead>
<tr>
<th>Types of Trachelectomy</th>
<th># of patients</th>
<th>Recurrence (n)</th>
<th>Deaths (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Trachelectomy</td>
<td>845</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>10 studies</td>
<td></td>
<td></td>
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<tr>
<td>Abdominal Trachelectomy</td>
<td>244</td>
<td>7</td>
<td>0</td>
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<tr>
<td>10 studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic Trachelectomy</td>
<td>57</td>
<td>2</td>
<td>2</td>
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<tr>
<td>7 studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robotic Trachelectomy</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6 studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
  - Lymphvascular 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
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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Disclosure

- I have no relationships or financial compensation from any drug companies or industries
Fertility after cervical cancer surgery

- **Scope of surgery**
  - **Cone biopsy, LEEP**
    - Should have minimal impact on fertility unless complicated by uterine scaring 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
Speiser et al, Int J Gynecol Cancer, 2011
Fertility after cervical cancer surgery

- **Tracheolectomy**
  - 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

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

Buekers, Gynecol Oncol, 2001
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 Gy will kill ~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 ~40 Gy
  - In young women, 10-20 Gy may induce premature menopause
  - In older reproductive age women >40, only 6 Gy may induce premature menopause
- Risk of ovarian failure is almost certain after radiation

Sklar et al, J Natl Cancer Inst Monogr, 2005
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

- **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

<table>
<thead>
<tr>
<th>Thawed Embryos From Non-Donor Oocytes</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Transfers</td>
<td>11858</td>
<td>5865</td>
<td>4411</td>
<td>1521</td>
<td>1088</td>
</tr>
<tr>
<td>Percentage of transfers resulting in live births</td>
<td>38.7</td>
<td>35.1</td>
<td>28.5</td>
<td>21.4</td>
<td>15.3</td>
</tr>
<tr>
<td>Average number of embryos transferred</td>
<td>1.9</td>
<td>1.9</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Percentage of live births with twins</td>
<td>32.4</td>
<td>27.2</td>
<td>22.1</td>
<td>16.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Percentage of live births with triplets or more</td>
<td>1.5</td>
<td>1.5</td>
<td>1.1</td>
<td>1.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

- 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

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

<table>
<thead>
<tr>
<th>Donor Oocytes (all ages)</th>
<th>Thawed Embryos</th>
<th>Fresh Embryos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Transfers</td>
<td>6183</td>
<td>9321</td>
</tr>
<tr>
<td>Percentage of transfers resulting in live births</td>
<td>34.8</td>
<td>55.6</td>
</tr>
<tr>
<td>Average number of embryos transferred</td>
<td>2.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

2010 SART data, www.sart.org
### Success rates with gestational carriers

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles</td>
<td>300</td>
<td>184</td>
<td>231</td>
<td>101</td>
<td>43</td>
</tr>
<tr>
<td>Percentage of cycles resulting in pregnancies</td>
<td>55.3</td>
<td>46.2</td>
<td>39.4</td>
<td>28.7</td>
<td>20.9</td>
</tr>
<tr>
<td>Percentage of cycles resulting in live births</td>
<td>48.7</td>
<td>38.0</td>
<td>29.9</td>
<td>16.8</td>
<td>4.7</td>
</tr>
</tbody>
</table>

- 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

2010 SART data, www.sart.org
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