ONCOFERTILITY
for Gynecologic Oncologists

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In recent years, the survival of young cancer patients has improved markedly along with advances in multidisciplinary treatment, but many patients face infertility as a result of their gonadotoxic treatment.
Cancer Therapy and Loss of Fertility

**Radiation Therapy**
- Whole body irradiation: Testicular, ovarian, uterine
- Whole abdomen: Ovarian
- Pelvis: Ovarian
- Brain: Testicular, ovarian

**Chemotherapy**
- Alkylating agent: Testicular, ovarian
- Platinum: Testicular
Discussing oncofertility: The oncologist’s responsibility

- Fertility preservation is an important issue among patients diagnosed with cancer during or before their reproductive years.
- About 75% of patients without children at the time of their cancer diagnosis wish to have future offspring.
- Despite concerns about fertility among patients undergoing potentially sterilizing cancer treatments, oncologists may not always be discussing options for fertility preservation with their patients.
A new discipline that bridges oncology and reproductive medicine in order to discover and apply new fertility preservation options for young patients with fertility-threatening diseases or treatments.

The Oncofertility Consortium® is a national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors. Initial funding was provided by the National Institutes of Health (http://nih.gov) through the NIH Roadmap for Medical Research/Common Fund (http://nihroadmap.nih.gov).

Survival rates among young cancer patients have steadily increased over the past four decades in part because of the development of more effective cancer treatments. Today, both women and men can look forward to life after cancer, yet many may face the possibility of infertility as a result of the disease itself or these lifesaving treatments.

We developed the Oncofertility Consortium® to address the complex health care and quality-of-life issues that concern young cancer patients whose fertility may be threatened by their disease or its treatment.

The Consortium was launched with a grant from the National Institutes of Health (http://nih.gov) and represents a nationwide, interdisciplinary, and interprofessional network of medical specialists, scientists, and scholars who are exploring the relationships between health, disease, survivorship and fertility preservation in young cancer patients. Their work and its findings may also extend to patients who have been diagnosed with other serious diseases and who must undergo fertility-threatening treatments.

Here, you'll find information about Oncofertility and the work of the Oncofertility Consortium, as well as resources that will help you navigate the complex fertility issues facing patients with cancer and other serious diseases.

- Teresa K. Woodruff

Oncofertility is an interdisciplinary field at the intersection of oncology and reproductive medicine that expands fertility options for cancer survivors.
Chemotherapy related amenorrhea (CRA)

“Amenorrhea for three months or longer occurring within one year from the start of therapy.”

The incidence: **20 to 100%**.

(Bines J et al. JCO 1996)

The incidence depends on

1. the **age** of the patient
2. the **types of anticancer agents** used
3. the **doses** of the anticancer agents
The loss of ovarian function due to treatment of young cancer patients with chemotherapy and/or radio therapy:

Problem

◆ loss of fertility
◆ early onset of menopause
◆ climacteric disorders
◆ osteoporosis

The QOL of the patients as a woman decreases!!
Alkylating agents have long been considered the anticancer agents associated with the highest risk of chemotherapy-related amenorrhea.
“As part of education and informed consent prior to cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists.”
### Table 2. Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Cancer Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (&gt; 80%)</td>
<td>Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan</td>
</tr>
<tr>
<td></td>
<td>External beam radiation to a field that includes the ovaries</td>
</tr>
<tr>
<td></td>
<td>CMF, CEF, CAF × 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>AC × 4 in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td>CMF, CEF, CAF × 6 cycles in women age 30-39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)</td>
</tr>
</tbody>
</table>

*These are general guidelines based on best available literature. Additional factors, particularly pre-treatment ovarian reserve, specific treatment regimen, and age determine individual risk for immediate infertility, or for premature ovarian failure after resumption of menses. Please see text for details."
In 2006, ASCO published Recommendations for Fertility Preservation in People Treated for Cancer to inform oncologists of available preservation options and to guide them through the discussion and referral processes. However, according to the data presented at the ASCO Annual Meeting, only 38% of oncologists were aware of the recommendations.

When discussing fertility preservation, the guidelines recommend that infertility be discussed as a potential risk of cancer therapy — much like cognitive or cardiac complications — because infertility can affect survivors indefinitely, sometimes making future reproduction virtually impossible.

Although ASCO’s recommendations encourage oncologists to use their clinical judgment to determine the best time to inform patients about fertility preservation, they also emphasize the importance of discussing and referring patients to specialists at the earliest possible opportunity to allow men to collect samples and women to undergo egg or embryo cryopreservation.
• A systemic review and *meta-analysis* of 13 studies (3 randomized controlled trials and 10 non-randomized studies) showed that GnRH agonist treatment resulted in a higher likelihood of preserved ovarian function.

• However, when they limited the analysis to only randomized-controlled trials, there was no statistically significant difference.
Reproductive options AFTER cancer

• **Pregnancy Rates After Cancer**
  Several factors need to be accounted for when predicting the change of future pregnancy when banking embryos or eggs.

• First of all, one must consider the anticipated 'success' of a controlled ovarian stimulation (COS) procedure, in terms of stimulation characteristics, oocyte yield, fertilization rates, etc. Next, it is important to predict actual pregnancy rates from cryopreserved oocytes or embryos per transfer cycle.
Assessing Ovarian Reserve After Cancer Treatments

What does the literature tell us?

• Many prior studies have looked at this issue. However, many of these studies were retrospective, and most specifically address menstrual cycles, not fecundity.

➢ To date, there is no prospective data specifically addressing likelihood of infertility after cancer treatments.
Natural Decline of Ovarian Reserve and Effect of Anti-cancer Treatment
Chemotherapy for breast cancer

- 41% of women experience an initial 6 month period of CIA (chemotherapy induced amenorrhea) after chemotherapy
- Patients are more likely to ‘recover’ menses after AC or ACT compared to CMF
- Age is a significant predictor of amenorrhea at 6, 12, and 24 months
  - Women are 25X more likely to have at least 6 months of amenorrhea if they are >40 versus ≤35
  - Only 11% of women age 20-34 had a 6 month period of amenorrhea, regardless of chemotherapy regimens
- If a woman has 24 months of amenorrhea after chemotherapy, her chance of resumption of menses is:
  - 10% overall
  - 0% after CMF
  - 15-26% after AC or ACT
- Limitations of this study include the fact that there is no info about exact doses of chemotherapy and no info about fertility (or hormone testing)
- May be helpful when deciding when to switch from tamoxifen to aromatase inhibitors.

Childhood Cancer Survivor Study

• Acute ovarian failure was more common in children who received:
  – Doses of >10 Gy radiation to the pelvis
  – Older children receiving alkylating agents or procarbazine

• Premature menopause, defined as cessation of menses before age 40.
  – Compared to their siblings childhood cancer survivors had a significantly higher likelihood of premature menopause (0.8% vs 8%, respectively, RR 13.2, 95% CI 3.2, 53.5).
  – Rates were higher in survivors who were older, had exposure to increasing doses of pelvic radiation, had a higher alkylating score (more agents and cumulative dose), and had a diagnosis of Hodgkin’s lymphoma.

Models to predict premature menopause?

- **Prior Radiation Therapy**
- With radiation therapy, it is possible to determine the effective dose of radiation received by the ovaries with relative precision. Wallace et al. attempted to model the chance of premature menopause, based on the dose of radiotherapy and the woman's age.
- To date, these results have not been validated prospectively in a cohort of women receiving radiation.
- Nonetheless, attempting to predict premature menopause is a useful clinical tool, giving patients and providers a general estimate of the risk of radiation based on dose and age.

Models to predict premature menopause?

- Prior Chemotherapy
- Predictive models are difficult with chemotherapeutic agents. There are so many types of medications, protocols/combinations, dosing variations that it is impossible to estimate the dosage received by the ovary and reliably predict the degree of follicular damage.
- To date, there are no models for to predict ovarian reserve after chemotherapy.
What does the presence or absence of menses indicate?

- If the patient is NOT having menstrual cycles, what does this mean?
- Evaluate for secondary amenorrhea. It may be premature ovarian failure, but this should be confirmed with lab tests (FSH, estradiol, or AMH). If these are normal, a full evaluation for secondary amenorrhea should be pursued.
If the patient IS having menstrual cycles, is she fertile?

• If she is interested in conception now, consider checking markers of ovarian reserve (FSH, estradiol, antral follicle count, or AMH).

• If she is not interested in a pregnancy now, she and her partner must use adequate contraception.
  – Contraception in women with a history of a hormone sensitive cancer can be tricky. Options include permanent sterilization (tubal ligation or vasectomy), copper IUD, or barrier contraception (condoms, etc).
  – It is definitely possible to ovulate on SERMs or aromatase inhibitors (such as tamoxifen or letrozole). Women need adequate contraception while taking these medications.
Logistics and Safety of Pregnancy After Cancer

• Reports about pregnancy after cancer treatments are rather limited. This may be because the proportion of reproductive aged women with cancer is relatively low. In addition, cancer survivors may not attempt pregnancy, due to fertility problems (amenorrhea) and/or fear of recurrence.
Safety of pregnancy: offspring

• One of the largest studies evaluating pregnancy outcomes in cancer survivors compared reproductive outcomes in men and women who had a history of childhood cancers as compared to their siblings\(^3\).

• The partners of males who had received childhood cancer treatments did not have adverse pregnancy outcomes, in general. Only treatment with non-alkylating chemotherapy increased the risk of low birth-weight offspring.

• Females who received childhood cancer treatments who specifically received pelvic radiation had offspring that were more likely to be premature, have a low birth-weight, and be small for gestational age. Receiving doxorubicin or daunorubicin increased the risk of low birth-weight, independently of pelvic radiation.

• There were no apparent differences in the risks of congenital abnormalities, single-gene defects, or cytogenic abnormalities in survivors of childhood cancer, regardless of type of prior treatment.
## Table 1. Genetic Disease in Offspring of Cancer Survivors and Sibling Controls

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Survivor Offspring (n = 6,129)</th>
<th>Sibling Offspring (n = 3,101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Cytogenetic abnormality</td>
<td>7</td>
<td>0.1</td>
</tr>
<tr>
<td>Single-gene (Mendelian) disorder</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Simple malformation</td>
<td>136</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Adapted from Green DM, Sklar CA, Boice JD, Jr., et al. **Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study.** *J Clin Oncol* 2009;27:2374-81.
Timing of pregnancy

• Data is limited about when it is safe to consider pregnancy after treatment for cancer. This decision is usually made in close collaboration between the patient, the oncology team, and the fertility specialist.

• One study looked at pregnancy outcomes and risk of recurrence in women who conceived after breast cancer diagnosis and treatment. They found a survival benefit in women who waited at least 2 years after diagnosis to attempt conception.\(^1\)
  

• In some cases, the team decides that waiting to consider pregnancy until the 5-year disease-free marker is prudent.
  
  – In young women, or women who banked eggs or embryos prior to chemotherapy, this time-frame will not dramatically affect pregnancy rates.
  
  – However, in women who will be in the late 30’s or 40’s when attempting conception (without banked eggs or embryos), five years may dramatically decrease chances of pregnancy. In these cases, women should be counseled about the possible additional benefit of egg/embryo banking, even in cases when they do not require chemotherapy.
Preservation of fertility in women

- Currently, cryopreservation technologies are the most commonly used and the most effective forms of fertility preservation, according to Oktay. Women undergoing infertility-producing treatment for breast cancer, hematologic malignancies and other solid tumor cancers have two cryopreservation options: embryo freezing and egg freezing.

- Embryo freezing is a good option for women who have a male partner or a donor they are willing to use. The technique works by stimulating the ovary to produce eggs that are fertilized in vitro and then stored for later use. The process takes two to six weeks, depending on where a woman is in her cycle.

- Women who may not have a partner, those who are not ready to select a donor, or women with religious concerns about the creation of embryos may prefer egg freezing compared with embryo freezing. The process is similar to embryo cryopreservation but involves freezing the egg itself. According to Duffy, although success rates are a bit lower with this technique compared with embryo freezing, progress has been made in this area.
Fertility preservation in infertility patients caused by cancer therapy

- Oocyte cryopreservation
- Sperm cryopreservation
- Embryo cryopreservation
- Ovarian tissue cryopreservation

Important Factors

1. the type of cancer and its stage of progression
2. the anticancer agents used for chemotherapy
3. the timing of starting chemotherapy
4. the patient's age
5. the marital status.
The period available for fertility preservation before starting anticancer therapy is often less than one month.

Therefore, even when in vitro fertilization and cryopreservation of embryos is performed, this is usually limited to only one course and is not satisfactory for lifetime fertility preservation.

In some patients, infertility treatment even has to be terminated during a cycle.
Fertility preservation method

Gynecological malignancy

Radiotherapy to pelvis

Chemotherapy and start of chemotherapy...

More than 2 weeks

Less than 2 weeks

Ovarian tissue cryopreservation and/or GnRHa

Estrogen dependent

Fertility-preservation surgery where possible

Ovarian transposition and/or ovarian tissue cryopreservation and/or ovarian stimulation and cryopreservation of fertilized and/or unfertilized oocytes

NO

Ovarian stimulation and cryopreservation of fertilized and/or unfertilized oocytes and/or ovarian tissue cryopreservation and/or GnRHa

YES

Ovarian tissue cryopreservation

Ovarian stimulation for cryopreservation of oocytes and GnRHa only after specific risk-benefit analysis

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Several studies have shown that the ovarian tissue can be successfully frozen and grafted in human (2004).

Ovarian cortex cryopreservation should be offered before gonadotoxic chemotherapy in all cases where there is a high risk of POI and where emergency IVF is not possible.

19 live births after transplantation of frozen-thawed ovarian tissue (Donnez J: International Ovarian Conference 2012, Tokyo, Japan)

Evaluation of the ovarian reserve in women transplanted with frozen and thawed ovarian cortical tissue

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a Laboratory of Reproductive Biology, Juliane Marie Centre for Women, Children and Reproduction, and b Fertility Clinic, Copenhagen University Hospital, Copenhagen; and c Department of Gynecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark

Objective: To investigate ovarian reserve and ovarian function in women transplanted with frozen/thawed ovarian tissue.

Design: Retrospective cohort study.

Setting: University hospital.

Patient(s): 18 women transplanted with their own frozen/thawed ovarian tissue.

Intervention(s): None.

Main Outcome Measure(s): Levels of antimülleraian hormone (AMH), duration of function of the transplanted ovarian tissue, outcome of assisted reproduction.

Results: Of the 18 women who received transplanted ovarian tissue, levels of AMH were measured in 12 women; AMH never exceeded a concentration of 1 ng/mL, and in several cases they were below the detection limit of the assay in combination with regular menstrual cycles. Two women with AMH below the detection limit conceived spontaneously. The duration of function of the transplants was between 0 months and 8 years and still functioning. Twelve women received ART in 72 cycles (65 oocytes were retrieved).

Twelve women received ART in 72 cycles (65 oocytes were retrieved).

Duration of graft function (first transplantation): median 26 mo (0 to 88 mo).

Fertilization rate: 40% (26 to 65).

Pregnancy rate: 6.9% (5 to 72).

Delivery rate: 2.8% (2 to 72).
The IRB of St. Marianna University School of Medicine approved Prof. Suzuki’s clinical study of transplantation using vitrified human ovarian cortex at the end of 2009.

2010. 1- Clinical application

In Liquid Nitrogen

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The 28th Congress of Korean Society of Gynecologic Oncology
Oncofertility

• A new discipline that bridges oncology and reproductive medicine.
• In order to discover and apply new fertility preservation options for young patients with fertility-threatening diseases or treatments.
• This is an urgent issue.
• We as Gynecologic Oncologists must play a key role in Oncofertility.
• I strongly recommend to establish Oncofertility Society in Asia.