Executive Summary

Purpose: To provide health care providers at Princess Margaret Cancer Centre information about fertility preservation options for female cancer patients and recommendations for care delivery.

Methods: A review of published literature from January 2000 to June 2014 was completed using MEDLINE. Formal, published guidelines by recognized associations were reviewed for recommendations.

Recommendations:

- All newly diagnosed cancer patients and patients beginning a new plan of care will be informed of the potential risk of the proposed treatment plan to their fertility as a standard part of a treatment consent discussion. Grade B.

- A reproductive specialist or health care provider should be involved to discuss FP interventions if a woman requests this information. Patients will be informed of FP options - both proven and unproven technologies. Grade C.

- The decision to pursue FP interventions is up to the patient and family; declining to pursue any intervention is acceptable. Grade C.

- Oocyte and/or embryo preservation are considered standard practice and should be offered to women at risk for infertility and requesting fertility preservation technologies. Grade A.

- Oocyte preservation should occur before the onset of cytotoxic therapy in patients at risk for acute ovarian failure (AOF). Grade A.

- Random start (menstrual cycle day-independent) techniques are available to minimize oncologic treatment delays; consideration of which ovarian stimulation technique to use, and subsequent impact on treatment delay, is dependent on local fertility clinic expertise. Grade B.

- Limited data is available assessing subsequent cancer risk in women with hormone sensitive cancers undergoing ovarian stimulation; however, there does not appear to be increased cancer recurrence risk as a result of stimulation protocols. Grade B.

- Providers with appropriate expertise should discuss other fertility preservation methods (such as ovarian transposition, conservative gynecologic surgery, conservative radiation therapy options and ovarian tissue cryopreservation and re-transplantation) if appropriate. Ovarian tissue cryopreservation and re-transplantation is considered experimental, this procedure should be undertaken in a clinical trial. Grade C.

- Given the absence of consensus in the literature, and lack of clear harm, the use of GnRH analogs may be considered in women in whom definitive fertility preservation is not possible. Grade A.
Guideline

1.0 Introduction

The purpose of this guideline is to guide healthcare providers about fertility preservation for female cancer patients with conditions or needing treatments that may place their fertility at risk.

Target Users
- Physicians, Nurse Practitioners, Nurses, Pharmacists and Social Workers.

Target Patient Population
- Women diagnosed with cancer ≤ 42 years of age.
- Patients requiring anti-cancer treatments that may put their fertility at risk, either due to direct effects of the treatment or the potential teratogenic effects of chronic anti-cancer treatment that delays child-bearing (e.g. tamoxifen).

2.0 Definitions

FP: Fertility Preservation
PMAYA: Princess Margaret Cancer Centre Adolescent and Young Adult Program

3.0 Clinical Practice Recommendations

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<td>B</td>
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<td>C</td>
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Adapted from Shekelle, 1999 [1]
3.1 Infertility Nomenclature

Primary hypogonadism is defined by low ovarian estrogen and progesterone levels. The two major categories of primary hypogonadism include acute ovarian failure (AOF) and premature (or primary) ovarian failure (POF) [2].

Patients who lose ovarian function during cancer therapy or shortly after its completion are classified as having acute ovarian failure (AOF). Patients, who retain ovarian function after therapy completion and then experience menopause before the age of 40, are classified as POF [2].

Secondary hypogonadism, or central hypogonadism, results from hypothalamic or pituitary defects, which subsequently impact gonadal function. Patients with secondary hypogonadism have low ovarian estrogen and progesterone levels, and serum LH and FSH concentrations that are inappropriately normal or low.

3.2 Estimation of Infertility Risk

Estimating the risk of infertility in women after cancer therapy depends on several patient factors including: cancer profile (type, site of disease), general health, baseline fertility and patient age at exposure. Treatment factors that influence fertility include: total cumulative dose of alkylating agents, cumulative gonadal toxicity of multi-drug chemotherapy regimens, radiotherapy field and dose, and surgery to organs with a contribution to fertility [3, 4]. The risk can be summarized as the chance of AOF with treatment, or POF in the years following treatment.

The known and potential fertility risks of all cancer treatments should be considered when counseling patients regarding fertility impact. The decision to pursue FP intervention may be influenced by the estimated risk to fertility [3].

Patients should be advised of the uncertainty regarding chemotherapy-related infertility estimates. Most data use return of menses as a surrogate for fertility, which in itself may not adequately estimate fertility.

3.3 Gonadotoxicity versus Teratogenicity

In addition to agents with gonadotoxic potential, consideration of the impact of agents with teratogenic potential should be given. For example, among pre-menopausal women requiring adjuvant endocrine therapy, tamoxifen is a commonly used medication. Although, tamoxifen does not have direct gonadotoxic potential, the agent is teratogenic and women taking this medication should not attempt pregnancy. As tamoxifen is used from 5-10 years in the adjuvant setting; women are affected by the negative impact of increasing age on fertility [4].

Women requiring: (1) treatments that delay childbearing or (2) treatments with unknown impact on gonadotoxicity or teratogenicity should be counseled accordingly. Specifically, the woman’s anticipated age at the end of treatment may impact the decision to pursue FP interventions.
3.4 Disclosure of Infertility Risk and Consideration of Referral to Reproductive Specialist

- All newly diagnosed cancer patients and patients beginning a new plan of care will be informed of the potential risk of the proposed treatment plan to their fertility as a standard part of a treatment and consent discussion [3]. Grade B.
- Patients may require immediate initiation of cancer therapy or may be too ill to undergo FP procedures. A patient should be informed of her potential risks of cancer treatment to her fertility and be made aware of the reason(s) why she is not a suitable candidate for FP interventions.
- Documentation of this fertility discussion into the patient chart, prior to onset of treatment, should take place. Grade C.
- A reproductive specialist or health care provider should be involved to discuss FP interventions if a patient requests this information. Grade C.
- Patients will be informed of FP options - both proven and unproven technologies [3]. Grade C.
- The decision to pursue FP interventions is up to the patient and family; declining to pursue any intervention is acceptable. Grade C.

3.5 Fertility Preservation Interventions

- A reproductive specialist or health care provider should be involved to discuss specific FP interventions if a patient requests this information. Grade C.

3.5.1 Options for Females

- Embryo and/or Oocyte Preservation
  - Oocyte and/or embryo preservation can be offered prior to cancer therapy or following the completion of cancer therapy [3]. A 6-12 month washout is recommended post therapy. Grade C.
  - Oocyte preservation should occur before the onset of cytotoxic therapy in patients at risk for acute ovarian failure AOF [3]. Grade A.
  - Oocyte and embryo preservation are suitable for post-pubertal females and are both considered established, non-experimental FP methods. Grade A.
  - Depending on the phase of the patient’s menstrual cycle, oocyte preservation may take 2 weeks to complete. This option may not be suitable for patients with clinical conditions that preclude a delay in starting therapy [4-7]. Grade B.
  - Controlled ovarian stimulation requires daily subcutaneous injections for 9-13 days.
  - Oocyte retrieval requires multiple transvaginal ultrasounds and blood tests, and transvaginal aspiration under mild sedation.

- Embryo Preservation
  - Embryo preservation requires sperm (either from a partner or sperm bank) [3, 4].

- Oocyte Preservation
  - Oocyte preservation is an option for patients who do not have access to donor sperm or have ethical or religious objections to embryo preservation [8].

- Refer to a local Fertility and Reproductive Health clinic (link to referral form).
- Cost associated with these procedures is the responsibility of patient/family. Financial assistance may be available to families who qualify (link to Fertile Future application).
Transmittable disease screening (Syphilis Screen – VDRL, Hepatitis C Virus Serology, Hepatitis B surface antigen, HIV1/HIV2 serology) will be required.

- **Ovarian Suppression Therapy**
  - Gonadal protection through hormonal manipulation with gonadotropin-releasing hormone (GnRH) analogs for FP in women treating with gonadotoxic chemotherapy has demonstrated conflicting results [5, 9-20].
  - Published clinical guidelines from clinical associations engaged in FP conflict in their recommendations regarding GnRH analogs. The American Society of Clinical Oncology does not support the use of GnRH analogs however the Canadian Fertility and Andrology Society supports their use in FP [5, 21]. Many meta-analyses have been completed, some of which demonstrate a potential beneficial effect.
  - Patients and families should be made aware of this treatment and the conflicting data in the literature regarding the use of GnRH analogs to protect ovarian function.
  - Given the absence of consensus in the literature, and lack of clear harm, the use of GnRH analogs may be considered in women in whom definitive fertility preservation is not possible. **Grade A.**
  - If undertaken, administration of GnRH analogs should be undertaken by prescribing oncologists, as per the available literature, to coordinate with systemic therapy administration.

- **Ovarian Transposition (oophoropexy)**
  - Oophoropexy is a treatment strategy to move ovaries away from the radiation field when pelvic radiation is performed as part of cancer treatment [4, 5].
  - Due to radiation scatter, ovaries are not always protected and patients should be advised of the possibility of lack of success [5].
  - The procedure should be performed as close to the time of radiation treatment onset due to risk of migration of the ovaries.
  - There is controversial data regarding the efficacy of this procedure [4, 22].
  - There is risk to the blood supply of the ovary during this procedure [4, 22] which in itself may diminish ovarian function over time.

- **Conservative gynecologic surgery and radiation therapy options**
  - Conservative gynecologic surgery is a strategy utilized to spare fertility by performing less radical surgeries with the intent of sparing as much of the reproductive organs as possible.
  - Such strategies have been employed in early stage cervical, ovarian and endometrial cancers [4, 23].
  - Such strategies should be discussed with all eligible patients. In situations where such strategies are inappropriate, a patient should be informed why she is not a suitable candidate.
  - Shielding of the gonadal regions is standard procedure for reducing scatter radiation and ovarian damage [4].
Fertility Preservation in Female Cancer Patients

- **Ovarian tissue cryopreservation and re-transplantation**
  - This technique is considered experimental. The use of tissue for successful attainment of pregnancy is an unproven technology. Consideration for this procedure should be undertaken in a clinical trial.
  - Referred patients must be medically fit and able to undergo a laparoscopic abdominal procedure.
  - Ovarian tissue cryopreservation and future transplantation is a potential option for women who are unable to achieve oocyte retrieval.
  - This technique may be considered, particularly in women undergoing pelvic surgery who are destined to have adjuvant pelvic RT.
  - There are concerns with reintroduction of cancer cells with re-implanted ovarian tissue; this procedure is contraindicated in patients with leukemia.

3.5.2 Fertility Preservation Risks

- **Hormone Sensitive Cancers**
  - Concern has been raised in hormonally sensitive malignancies (such as estrogen-sensitive breast and gynecologic malignancies) that FP interventions (e.g. ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence.
  - Limited data, limited by selection bias and short-term follow-up, is available; current studies do not indicate increased cancer recurrence risk as a result of stimulation protocols [24].

  
  Grade B.

3.5.3 Fertility Preservation Logistics

- **Timing of Fertility Treatment**
  - Oncology treatment delays are commonly associated with FP techniques.
  - Ovarian stimulation protocols utilized for oocyte and embryo preservation are dependent on local expertise. Local stimulation techniques currently utilized include menstrual cycle day-independent (random stimulation) techniques; thus, women may not need to be at the beginning of a menstrual cycle at the time of stimulation. Random stimulation is currently a newer technique with less supporting evidence.
  - Timing decisions will be made by the local fertility clinic with input from the treating oncologist regarding urgency of treatment.
  - Most women will not have enough time to pursue more than one cycle of harvesting. Should the first cycle fail or lead to poor oocyte retrieval, additional cycles will further delay oncologic treatment.
  - Patients should be seen within 72 hours of referrals to fertility specialists to minimize delays.

- **Typical Ovarian Simulation Protocol**
  - IVF stimulation protocols generally involve the use of 3-4 types of drugs:
    1. A medication to suppress the luteinizing hormone surge and ovulation (until the developing eggs are ready). A GnRH-agonist (gonadotropin releasing hormone agonist) such as Lupron or GnRH-antagonist may be used.
    2. A follicle stimulating hormone (FSH) product to stimulate development of multiple eggs.
    3. An LH containing product may be added to the regimen.
    4. Human chorionic gonadotropin (HCG) to cause final maturation of the eggs.
Fertility Preservation in Female Cancer Patients

- Typical Timelines a patient may experience are as follows:
  - Baseline tests are conducted prior to any treatment. A baseline ultrasound examination and a blood test (usually for FSH, estradiol and antimullerian hormone (AMH)).
  - Cycle day is determined by the IVF clinic.
  - Day 3 – 12: Ovarian Stimulation. Daily injectable fertility medications begin on a day that is chosen by the cycle coordinator.
  - Day 5 after stimulation – Cycle Monitoring. Regular office visits start and are continued every one to two days until follicle aspiration.
  - Day 8 to 12 after stimulation – Ovulation Induction. Ovulation is triggered with an injection of HCG, or a GnRH agonist, administered when the follicles are judged to be mature based on ultrasound and hormone criteria.
  - 36 Hours after HCG – Egg Retrieval. Women will undergo an aspiration procedure that takes less than 30 minutes. Women will arrive at the clinic one hour before the scheduled retrieval procedure and go home approximately two hours afterwards.

- Likelihood of Success
  - Embryo and oocyte preservation success rates are specific to individual fertility clinics. Subsequent successful pregnancies are dependent on the quality of the eggs, which is inversely related to female age. Success is also related to the thawing process, the ability to fertilize the thawed oocyte (for those who underwent oocyte preservation alone) and the ability of the implanted embryos to develop into pregnancies.
  - Embryo: The overall IVF clinical pregnancy rate in Canada is 32% per cycle started, 34% per egg retrieval procedure, and 39% per embryo transfer procedure. This does not take into account the thawing process [25].
  - Oocyte: Success rates are clinic dependent and decline with age. Overall pregnancy rate ranges from 7-25% [26].

- Costs of Treatment
  - Financial costs associated with fertility treatments are specific to the procedures undertaken, including number of cycles of harvest, medications required and the individual fertility clinic.
  - Certain clinics offer discounted rates for oncology patients.
  - Average costs for oocyte preservation and embryo preservation can range from $5,000 - $7,000 CAD. Costs from medications are additional and may be covered by private drug plans.
  - Financial assistance may be available to families who qualify (link to Fertile Future application)
### 3.5.4 Fertility Preservation Strategies

**Table 2: Fertility Preservation Strategies Dependent on Type of Treatment**

<table>
<thead>
<tr>
<th>If the treatment includes:</th>
<th>Consider the following Options:</th>
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<tbody>
<tr>
<td>Cancer Surgery</td>
<td>1. Fertility sparing surgery (gonad preservation)</td>
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<tr>
<td></td>
<td>2. Uterus preservation</td>
</tr>
<tr>
<td></td>
<td>3. Cryopreservation if high risk of gonadal damage anticipated</td>
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<tr>
<td>Radiation Therapy to pelvis and gonads</td>
<td>1. Shielding to reduce damage to ovaries</td>
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<td></td>
<td>2. Ovarian transposition</td>
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<tr>
<td></td>
<td>3. Cryopreservation if high risk of gonadal damage anticipated</td>
</tr>
<tr>
<td>Cytotoxic Treatment with high gonadotoxicity</td>
<td>1. Cryopreservation</td>
</tr>
<tr>
<td>Endocrine Therapy for estrogen sensitive breast cancer</td>
<td>1. Cryopreservation if age at completion of treatment is at a time when natural fertility is likely low</td>
</tr>
<tr>
<td></td>
<td>- &gt; 33 years of age at start of treatment if 5 years planned</td>
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<td></td>
<td>- &gt; 28 years of age at start of treatment if 10 years planned</td>
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Adapted from Rodriguez-Wallberg and Oktay, 2014 [4]
3.5.5 Fertility Preservation Pathway

Start: Cancer Diagnosis

- Seen by Oncology Team
- Team Discusses Fertility Risk

Decision to see Fertility Specialist

- Info entered on chart
  - No
  - Yes or Unsure
    - Complete lab work (to submit with referral)
      - Fertility Referral Sent
      - Seen by Fertility Clinic

Figure 1: Princess Margaret Cancer Centre
Fertility Preservation Process
Fertility Preservation in Female Cancer Patients

Decision for Fertility procedure

- Yes: FP Procedure → Routine Oncologic Care → End: Follow-up Care
- No: Info entered on chart

Notes:

1 Eligible Patients: women < 45 years; men < 65 years
2 Regardless of fertility risk
3 AMH level, VDRL (syphilis screen), Hepatitis C serology, Hepatitis B antigen, HIV serology
4 Follow-up Care: women → ovarian function checks (frequency to be determined); men → yearly semen analysis

Contacts

Princess Margaret Cancer Centre AYA Program
Email: aya@uhn.ca; Phone: 416-946-4501 ext. 5579
4.0 Implementation

Facilitators to implementation
- The Princess Margaret Cancer Centre Adolescent and Young Adult Program (PMAYA) is available for consultation to patients and families and to facilitate FP procedures. Although the program formally assesses patients < 40 years of age, referrals will be accepted for older patients who may be candidates for FP. The team may be reached at aya@uhn.ca
- The PMAYA is conducting research investigating methods to improve the delivery of information to patients and families regarding FP.
- The PMAYA is educating clinicians about FP options for patients.

Organizational barriers to implementation
- It has been reported in the literature that patients are dissatisfied with the FP discussions that occurred at the time of their diagnosis [27, 28]. It is also identified in the literature that health care providers do not consistently deliver FP information to all patients at risk [29-31].
- A specific fertility clinic is not recommended; however, women referred to fertility specialists should be seen within 72 hours of referral.

Potential economic impact
- Cryopreservation of oocytes, embryos and ovarian tissue will require additional procedure and clinic time at fertility clinics in addition to storage facilities. Appropriate infrastructure support will be needed to ensure the necessary resources are in place.

Key review criteria/indicators for monitoring and audit purposes
- The PMAYA will track the number of consultations and procedures performed annually. Plans are underway to assess family/patient satisfaction with FP services. Educational modules for healthcare practitioners will also be developed, implemented and evaluated.

5.0 Related Documents
- Fertility clinic referral form
- Power of Hope referral form
- Cancer Knowledge Network: Oncofertility Referral Network

6.0 Statement of Evidence

This document was drafted by Amirtha Srikanthan, MD, and reviewed and approved by Drs. Abha Gupta and Ellen Greenblatt. This guideline is based on a search of relevant literature published in the last 10 years. The recommendations in the guideline are based on the guidelines published by the American Society of Clinical Oncology for fertility preservation in cancer patients. The level of evidence for this guideline is grade B/C.

This guideline will be reviewed by the PMAYA every two years. As new information becomes available, this guideline will be updated as appropriate. The authors declare no conflict of interest.
7.0 References

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