Commentary

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Guidelines for Fertility Preservation in Gonadotoxic Treatment Patients

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Description

The management of young patients with cancer presents several unique challenges. In general, these patients are ill prepared for the diagnosis and the impact on their fertility. With the improved survival for all tumour types and stages, the need for adequate fertility counselling and a multidisciplinary approach in the reproductive care of these patients is paramount. Recent advances in cryopreservation techniques allow for the banking of spermatozoa, oocytes, embryos and ovarian tissue without compromising survival. This Canadian Fertility and Andrology Society (CFAS) guideline outlines the current understanding of social and medical issues associated with oncofertility and the medical and surgical technologies available to optimize future fertility. In Canada, 200,000 people are diagnosed with cancer annually. Long-term survival rates for many cancers are continually improving, with 5-year survival rates of over 80% for children and adolescents and over 70% for adults between 20 and 49 years of age. Survival often comes with a loss of reproductive function from gonadal toxicity. High-dose alkylating agents and ionizing radiation are particularly damaging, inducing sterility in a high proportion of patients. It is estimated that breast cancer affected more than 27,000 Canadians. Fifteen per cent of these individuals were of reproductive age, making it the most common malignancy in this age group and representing the bulk of referrals to Assisted Reproductive Technology (ART) facilities for fertility preservation.

Fertility preservation in cancer

Haematological (lymphoma and leukemia), colorectal, thyroid and testicular cancers, as well as melanoma, are among the most prevalent cancers among young Canadians. Rarely, gonadotoxic medications are needed for the medical treatment of individuals with autoimmune diseases such Systemic Lupus Erythematosus (SLE) and hematological disorders. The incidence of cancer in young people is low: 0.7% in children aged 0-14 and 1.5% in adolescents and young adults aged 15-29 years. One adult out of every 700 is thought to be a long-term survivor of childhood cancer. Special attention should be given to preserving fertility in children and adolescents, which will be covered individually in this recommendation. Most young cancer patients hope to have children in the future. Since the great majority of these patients live through their illness, it is imperative that they receive the multidisciplinary care and fertility counseling needed to address the intricate clinical and psychological issues they encounter. As anticipated, there is a correlation between age and the prevalence of early menopause, infertility and abrupt ovarian failure in chemotherapy patients. Even though this is not immediately evident with clinical and laboratory evaluation, at least a portion of ovarian reserve will be lost regardless of the type of chemotherapeutic drugs used. Chemotherapy changes the majority of objective indicators of ovarian reserve. In patients under 30, low-risk treatments for Hodgkin lymphoma, such as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine), seem to have short-term reversible effects on AMH concentrations in older patients. However, there are noticeable effects on both menstrual function and ovarian reserve testing. A shorter reproductive life can be anticipated even if regular menstrual cycles return, even if the patient is considered to be at "low risk" of experiencing an early menopause. Several recent investigations that performed successive AMH concentrations after chemotherapy concluded have shown that protocols used for breast cancer have a definite irreversible effect on the ovary. Assessments conducted at the 5- and 10-year marks revealed that the more aggressive regimen led to greater temporary amenorrhea and premature ovarian failure in a major prospective trial that randomly assigned patients to no, low-intensity or high-intensity chemotherapy.

Fertility risks post-treatment

A cumulative cyclophosphamide equivalent dose of alkylators as low as 4 g/m^2 is linked to an increased risk of early menopause in female survivors. The effect increases with increasing doses. Some of the finest information on fertility among childhood survivors to far has come from a big national Dutch nested-cohort research. Following exposure to several chemotherapeutic drugs, abnormal ovarian reserve testing is observed. Thankfully, they do not seem to affect either the future pregnancies or the genetic competency of the surviving oocytes. However, based on findings from mice, it would be worthwhile to postpone conception for 6-12 months following exposure due to potential short-term effects. Radiation produces free radicals, which damage DNA widely resulting in mutation, carcinogenesis, necrosis and apoptosis. Ionizing radiation's effects on the uterus and ovaries are related to the age at exposure and the effective dose (fractionation schedule), just like with chemotherapeutic drugs. Age affects the ovary's

effective sterilizing dosage. The birth weight was 20.3 Gy, the ages were 18.4 Gy at 10, 16.5 Gy at 20 and 14.3 Gy at 30. This is in contrast to the usual doses of 50 Gy for gynecological cancers and 10-12 Gy for total-body irradiation for a hematopoietic bone marrow transplant. Sterilizing dosages have been shown in certain trials. According to the DCOG LATER study, children who survived spinal radiation and complete body irradiation had a lower ovarian reserve and the effects of abdominal and pelvic radiation were dose-dependent. Concurrent pregnancy is another risk factor for early ovarian failure.