EUROPEAN HEMATOLOGY ASSOCIATION

Fertility preservation in patients with hematological malignancies - Section 1

The effects of chemotherapy and radiotherapy on reproduction

W. Hamish Wallace

University of Edinburgh & Royal Hospital for Sick Children, Edinburgh, United Kingdom

Take-home messages

- More high quality research is required to provide the evidence for impaired testicular and ovarian function after chemotherapy and radiation.
- Conditioning treatments for BMT that include chemotherapy and or radiotherapy are likely to impair gonadal function irrespective of the age of the patient at treatment.
- Radiotherapy to a field that includes the uterus in females may impair uterine function with increased risk of miscarriage and preterm delivery.

Introduction

With increasing numbers of childhood cancer survivors, it has become important to understand the effects of successful treatment on the gonads (ovaries and testes) and reproduction. In the male treatment with chemotherapy, radiotherapy, or surgery that involves the testis can cause impaired spermatogenesis, testosterone deficiency, and physical sexual dysfunction in young adult cancer survivors. In the female, some patients are at risk of premature ovarian insufficiency (POI) as a direct consequence of successful cancer treatment and those that have been exposed to radiation to a field that includes the uterus, particularly in childhood, are at risk of miscarriage and preterm labor.[1-6]

The ovary

The human ovary establishes several million non-growing follicles (NGF) at around five months of gestational age, which is followed by a decline to the menopause when approximately 1,000 remain at an average age of 50-51 years. With approximately 450 ovulatory monthly cycles in the normal human reproductive lifespan, this progressive decline in NGF numbers is attributed to follicle death by apoptosis. Recently we have identified the first model of human ovarian reserve from conception to menopause that best fits the combined histological evidence. This model allows us to estimate the number of NGF present in the ovary at any given age (Figure 1) and suggests that 81% of the variance in NGF populations is due to age alone. We have also demonstrated than the rate of NGF recruitment increases from birth to age 14 years then declines with age until the menopause.[5]

Radiation and the ovary

The ovaries may be damaged by radiation to a field that includes the pelvis (e.g. total body irradiation (TBI), abdominal or pelvic irradiation) and the magnitude of the effect is related to the radiation dose, fractionation schedule and age at time of treatment.[7] The human oocyte is exquisitely sensitive to radiation, with an estimated LD_{50} (the lethal dose required to destroy 50% of oocytes) of less than 2 Gy. Using our understanding of the effect of radiotherapy on the human oocyte we can estimate the age at POI and the estimated sterilizing dose following any given dose of radiotherapy at any given age.[8] This will not only provide a useful basis for clinicians to provide accurate information when counselling women about fertility following treatment for childhood cancer, but also will help clinicians to select the patients at highest risk of POI for ovarian cryopreservation. Gonadotrophin insufficiency after cranial irradiation (>24 Gy in the treatment of brain tumors) will often be manifest as delayed onset of puberty or absent menses and can be treated by sex steroid replacement therapy. Gonadotrophin insufficiency can also be treated with gonadotrophin replacement which will restore fertility.

Chemotherapy and the ovary

Chemotherapy treatment in premenopausal women is associated with an increased risk of premature ovarian insufficiency

(POI) but the exact mechanism through which this occurs is uncertain.[8] Ovarian damage is drug and dose dependent and is related to age at time of treatment, with progressively smaller doses required to produce POI with increasing age. The age-related difference is most likely to be due to older women having a smaller primordial follicle reserve at the start of treatment compared to young women, so that loss from a smaller follicle pool is more likely to induce POI.[4]

Chemotherapy treatment that is gonadotoxic (e.g. alkylating agents) appears to have two distinct effects on ovarian function. A direct effect on the primordial follicle pool and an immediate effect on growing follicles. The first is immediate, occurring during treatment, and is characterized by amenorrhea and results from loss of the growing follicle population. However, provided that sufficient primordial follicles remain in the resting pool upon the cessation of treatment, the population of growing follicles will then be replenished, and menses resume. Depending on the extent of the loss of the primordial follicle pool, POI and amenorrhea may result at a later date.[9] Where there is only partial loss of primordial follicles, this longer-term effect may not manifest itself until years or even decades after treatment, when the patient then undergoes POI. If there is in addition a direct effect on the primordial follicle pool the patient undergoes POI manifest by permanent amenorrhea shortly after treatment.[10]

Radiation and the uterus

It is important to remember the uterus when discussing the effects of cancer treatment in young women. The uterus is at substantial risk of damage following radiation to a field that includes the pelvis, in a dose and age dependent manner. Uterine function may be affected by doses of 10-30 Gy probably as a result of a direct effect on the uterine vasculature and musculature elasticity. We have shown impaired uterine growth and blood flow after TBI (14.4Gy)[11] and a recent study has confirmed that survivors who received pelvic radiation are at increased risk of preterm delivery. Pregnancy in survivors of childhood cancer who have received radiotherapy to a field that includes the uterus should therefore be considered as high risk, essentially related to uterine dysfunction.

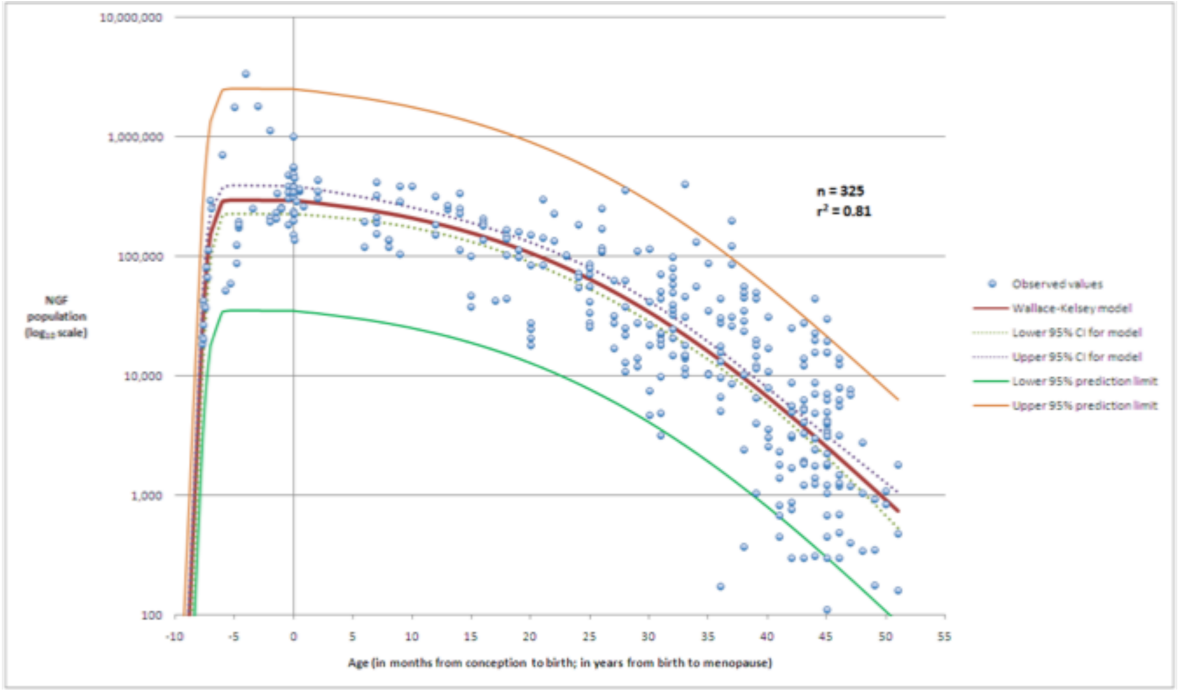

Figure 1. The best model for the establishment of the NGF population after conception, and the subsequent decline until age at menopause is described by an ADC model. The figure shows the dataset (n=325), the model, the 95% prediction limits of the model, and the 95% confidence interval for the model. The horizontal axis denotes age in months up to birth at age zero, and age in years from birth to 51 years.[6]

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The testis

Normal physiology

The seminiferous epithelium of healthy infant and child testes consists of immature Sertoli cells and spermatogonia. Spermarche occurs at a median age of 13.4 years (range 11.7-15.3) at a time when median testicular size is 11.5 ml (range 4.7-19.6). The pre-pubertal testis is approximately 2 ml in volume. The onset of puberty begins with enlargement of the testis at approximately 11.4 years. The healthy adult testis volume is 15-25 ml. Azoospermia may be present if the volume of each adult testis is 10 ml or less in a patient treated in childhood. As the endocrine function of the testis (Leydig cell activity) is relatively independent of Sertoli cell function and spermatogenesis, spontaneous progression through puberty is not a guarantee of future fertility.[12]

Radiotherapy to a field that includes the testis

Radiation has adverse effects on gonadal function in all males irrespective of their pubertal stage at the time of treatment. The degree and persistence of the damage is dependent on the dose, the treatment field and the fractionation schedule. Spermatogenesis is susceptible to irreversible damage at very low doses of irradiation (>1.2 Gy). However, Leydig cells are more resistant to damage from radiation and is usually preserved in doses up 20 Gy in pre-pubertal boys and 30 Gy in sexually mature men.[13] Progression through puberty with normal serum testosterone is common, despite azoospermia or evidence of severe impairment to spermatogenesis. TBI as a conditioning regimen for stem cell transplantation causes azoospermia in approximately 80% of males.[14]

Chemotherapy and the testis

A recent systematic review[1] looked at the evidence for adverse effects of cyclophosphamide, chlormethine and procarbazine on spermatogenesis, and found that there was reasonable evidence for an increased risk of impaired spermatogenesis after treatment with busulfan and cyclophosphamide, or fludarabine and melphalan, hematopoietic stem-cell transplant (HSCT) conditioning, ifosfamide doses of more than 60 g/m^2. The risks of impaired spermatogenesis after treatment with cisplatin remain unclear, although a recent study suggests a significant detrimental effect on the chance of siring a pregnancy.[15] In this CCSS study of male survivors reduced likelihood of pregnancy was associated with upper tertile doses of cyclophosphamide (HR 0·60, 95% CI 0·51-0·71; p<0·0001), ifosfamide (0·42, 0·23-0·79; p=0·0069), procarbazine (0·30, 0·20-0·46; p<0·0001) and cisplatin (0·56, 0·39-0·82; p=0·0023).[15]

Fortunately, modern first line treatment of Hodgkin lymphoma in children and young people is unlikely to be sterilizing as most patients are no longer exposed to procarbazine and high cumulative doses of alkylating agents.

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