

Preserving the fertility of children with cancer

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Moving beyond the uncertainties of risk, and limited, often difficult, preservation options, will require consensus and collaborative research

The remarkable cure rates achieved in childhood cancer mean that large numbers of survivors are currently among the young adult population. However, the treatment that has achieved this success may have adverse effects in many organ systems, including the reproductive organs. These adverse effects may result from the impact of cytotoxic chemotherapy (alkylating drugs such as cyclophosphamide, ifosphamide, procarbazine and busulfan, in particular) on gametogenesis, from radiation damage to the gonads, or from radiation delivered to the hypothalamic–pituitary axis.

To preserve fertility, it is necessary to determine the risk of fertility impairment before instituting cancer therapy. Predicting the impact of treatment on reproductive function in individual children based on expected exposures is notoriously unreliable. Current tools, both biochemical and biophysical, are unsuitable for assessing actual reproductive impacts in prepubertal and peripubertal children. Even when pubertal onset and progression is apparently normal, the integrity of gametes may have been compromised. A case–control study of 33 male survivors of childhood cancer showed that only a third had normal semen quality, and even in those who were not azoospermic, there were significant differences from normal controls. Seven of 11 azoospermic young adults were prepubertal at treatment, implying that the prepubertal state does not afford protection.¹

Similarly, a study of young adult female survivors treated in childhood, all of whom had regular menses or had a history of normal menses if they were using combined oral contraception, revealed partial reduction in ovarian reserve as shown by elevated follicle-stimulating hormone (FSH) levels, lower anti-Mullerian hormone levels and smaller ovary size on ultrasound in those with spontaneous menstruation, and failure to elevate inhibin B levels in response to FSH stimulation in those using combined oral contraception.² On the other hand, pregnancies have been noted in individuals predicted to be sterilised by their exposures to cancer therapies.

The treatment protocols applicable to a child's particular diagnosis may suggest higher risk. Those exposed to dose-intensive regimes of cyclophosphamide³ and other alkylators, particularly those with Hodgkin's lymphoma treated with MOPP (mustine hydrochloride [nitrogen mustard], Oncovin [vincristine], procarbazine and prednisone) and other alkylator-intense regimens, including those with metastatic sarcomas, or bone marrow transplantation, are at increased risk. Others at higher risk are those who need pelvic or testicular irradiation, or total body irradiation before marrow transplantation.

At the other end of the spectrum, children about to commence therapy on low-intensity protocols, such as those used for low-stage Wilms' tumour or acute lymphoblastic leukaemia, are at minimal risk of infertility. However, a substantial proportion of children beginning treatment fall into an intermediate risk category for which prediction is fraught with inaccuracy. The cut-off of 7.5 g/m² of cyclophosphamide recommended by the Children's Oncology Group as the exposure level to trigger

screening for fertility is a reasonable approximation of elevated risk, but not a reliable predictor of outcome at the beginning of therapy.

Given the uncertainty of predicting fertility outcomes, what options exist for preserving fertility in children facing cancer therapy, and how should parents and patients be counselled?

Cryopreservation of semen and subsequent in-vitro fertilisation is the only standard option for postpubertal males, and spermarche is the watershed around which options for boys are defined. Spermarche typically is an early to mid-pubertal event and occurs before the ability to achieve ejaculation.⁴ In the mature adolescent, semen is usually obtained by masturbation, with electrostimulation or vibratory stimulation as alternatives (the latter two may be applicable in peripubertal boys). However, the rate at which viable samples are obtained is highly variable. These adolescents are often sick as well as embarrassed and uncomfortable. One study of 62 attempts by adolescents to bank sperm before therapy resulted in totally normal semen in only four.⁵ Adolescents may be more successful if unaccompanied by parents.⁶ The advent of intracytoplasmic sperm injection (ICSI) enables in-vitro fertilisation of ova with even single sperm and so, despite the low yield rate, semen cryopreservation should be encouraged — as appears to be the case in the survey of practice in Australia and New Zealand by Heath and Stern in this issue of the *Journal* (page 538).⁷ Whether ICSI will increase the incidence of abnormalities in the offspring of cancer survivors remains to be seen — the incidence of abnormalities in offspring of cancer survivors conceived by natural means is not elevated.^{8,9} However, ICSI may bypass the normal protective mechanisms which terminate abnormal embryos.

In adult men unable to produce semen for cryopreservation, harvesting of testicular sperm has been undertaken, either from testicular biopsy or percutaneous aspiration. However, in the presence of circulating cancer cells, breaching the blood–testicular barrier may pose the risk of testicular cancer recurrence analogous to the increased rate of central nervous system leukaemia after traumatic lumbar puncture. Of interest, even when sperm is banked, studies in adults suggest that a small proportion of men (10%–30%) retrieve and use the banked specimen.¹⁰

For prepubertal males, no current routine option exists. Approaches that may develop include testicular tissue cryopreservation, and germ cell cryopreservation and autografting. Both are entirely experimental at this time.¹¹

For female patients, the options are more limited. For mature women, oocytes can be harvested and fertilised, and resulting embryos preserved. However, this requires at least 2 weeks of hormonal preparation (daily injections of FSH), and an existing sperm source. Similarly, oocytes can be preserved and subsequently fertilised when a sperm donor is available, although success rates are lower.¹² Neither technique is applicable to children or adolescents. As ovarian tissue contains significant numbers of primordial follicles in younger females, the harvest-

ing and storage of ovarian tissue (preferably removed as ovarian cortical strips by laparoscopic techniques) before starting cancer therapy, with subsequent autotransplantation, is an experimental option. There is some evidence of successful restoration of hormone production and two reports of successful pregnancy.^{13,14} Which patients should be subjected to such invasive techniques needs clarification and consensus, and this procedure should only be undertaken under strict clinical trial conditions in centres with the necessary expertise. The risk of reintroducing cancer cells has not been accurately assessed, but is a real possibility.¹¹

In the face of uncertainty and limited options, many of which are invasive, the paediatric oncology community has been slow to embrace routine and consistent counselling of families about fertility preservation options. Heath and Stern have demonstrated this hesitation among Australian and New Zealand oncologists,⁷ and similar results have been obtained in North America.¹⁵

To be able to provide effective counselling and improve pre-emptive interventions to preserve fertility, paediatric oncologists must inform themselves of the options for their patients, forge links with paediatric endocrinologists and reproductive medicine specialists, define at-risk patients by consensus, and commit to participating in research in this area — as they have already done so well in the context of defining best cancer treatments.

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