Fertility preservation in children newly diagnosed with cancer: existing standards of practice in Australia and New Zealand

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ABSTRACT

Objective: To establish the extent to which sperm, oocyte and gonadal tissue collection and storage is offered to children newly diagnosed with cancer.

Design, participants and setting: A cross-sectional survey of all paediatric oncology services in Australia and New Zealand (ANZ) in December 2005.

Main outcome measures: Sperm, oocyte and gonadal tissue collection and storage practices at paediatric oncology services; comparisons with recently published North American practices and with current recommendations for best practice.

Results: 12 of the 13 centres (92%) completed the survey. All centres offered sperm preservation, but only 10 (83%) offered oocyte/ovarian tissue preservation. Two centres were using gonadotrophin-releasing hormone analogues for fertility protection in postpubertal females. Five (42%) had offered fertility preservation to patients before the completion of their sexual development. All centres were more likely to offer sperm preservation than oocyte preservation for any given disease. The most common diseases for which conservation was offered were lymphomas and sarcomas. The anticipated cumulative dose at which centres elected to offer fertility preservation varied widely, both for the alkylator cyclophosphamide (any to 10 g/m^2) and for abdominal/pelvic irradiation (any to 12 Gy) and spinal irradiation (any to 18 Gy). Fertility counselling was offered in a variety of settings by nine (75%) of the centres. Despite 11 centres (92%) agreeing that fertility preservation guidelines would be helpful, only two (17%) had guidelines in place.

Conclusions: There are inconsistencies in the indications for and methods of gamete conservation in paediatric oncology centres throughout ANZ. Variations in practice on a background of unresolved medical, legal and ethical issues suggest the development of guidelines would be helpful.

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About 750 children and adolescents are diagnosed with a cancer in Australia and New Zealand (ANZ) every year.[1] Fortunately, recent advances in treatment, including the widespread use of cooperative clinical trials, aggressive multimodality therapies, and improved supportive care, have led to a remarkable improvement in cure rates. Today, about 75% of these patients are expected to be long-term survivors.[2] Reintegration into society with a "normal" lifestyle and life experience is therefore one of the key aims of all paediatric oncology units. One aspect that continues to be a major concern in achieving this goal is fertility preservation.[3]

The risk of compromised fertility as a result of cancer therapy depends on multiple factors, including the age and sex of the patient, type of therapy, dose and duration of therapy, and type of tumour.[4] Fortunately, it is now possible for young people seeking to preserve their fertility to consider a range of therapeutic interventions. These include the use of gonadotrophin-releasing hormone (GnRH) analogues during chemotherapy in an attempt to protect the ovaries, gamete collection and freezing for subsequent artificial insemination or in-vitro fertilisation (IVF), freezing of ovarian tissue in the hope that oocyte harvest might be possible in the future, and surgical transposition of ovaries out of radiation treatment fields. However, many of these techniques remain experimental with, as yet, unproven benefits.[5] We aimed to establish the extent to which paediatric oncology units throughout ANZ are addressing the issue of fertility, and to determine whether the services being provided optimise the chances of its preservation. We also compared the Australian and New Zealand situation with recently published North American practices and current recommendations for best practice.

1 Participating Australian and New Zealand paediatric oncology centres

- The Children's Hospital at Westmead, Sydney, New South Wales, Australia
- John Hunter Hospital, Newcastle, New South Wales, Australia
- Mater Children's Hospital, Brisbane, Queensland, Australia
- Monash Medical Centre, Melbourne, Victoria, Australia
- Princess Margaret Hospital for Children, Perth, Western Australia, Australia
- Royal Children's Hospital, Brisbane, Queensland, Australia
- Royal Children's Hospital, Melbourne, Victoria, Australia
- Royal Hobart Hospital, Hobart, Tasmania, Australia
- Starship Children's Hospital, Auckland, New Zealand
- Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia
- Wellington Children's Hospital, Wellington, New Zealand
- Women's and Children's Hospital, Adelaide, South Australia, Australia ◆

METHODS

In December 2005, a cross-sectional email questionnaire was sent out to the 13 paediatric centres providing specialist oncology care in ANZ (Box 1).

We used a 17-item questionnaire based on a questionnaire previously administered to paediatric oncology centres in North America in the year 2000.[6] It covered: fertility preservation services, including counselling offered; doses of well described gametetoxic therapies at which a discussion of fertility preservation options is triggered; and presence and use of guidelines.

Questionnaires were distributed to the Children's Oncology Group (COG) and/or Australian and New Zealand Children's Haematology/Oncology Group principal investigator at each centre. These individuals were requested to either complete the

2 Existing practice for sperm and ova conservation

	Sperm collection and preservation		Ova collection and preservation	
	Australia and New Zealand	North America[6]	Australia and New Zealand	North America[6]
Centres offering conservation	12 (100%)	64 (93%)	10 (82%)	7 (10%)
Centres with established links to gamete collection and preservation services	11 (92%)	53 (77%)	9 (75%)	19 (27%)
Centres offering conservation to individuals before completion of sexual maturation	5 (42%)	10 (15%)	5 (42%)	2 (3%)

3 Sperm and ova conservation by tumour type*†

	Males		Females	
Disease	Australia and New Zealand	North America[6]	Australia and New Zealand	North America[6]
Hodgkin's lymphoma	100%	85%	64%	7%
Non-Hodgkin's lymphoma	100%	53%	55%	3%
Acute lymphoblastic leukaemia	45%	18%	9%	3%
Acute myeloid leukaemia	36%	30%	9%	3%
Wilms' tumour	0	7%	9%	2%
Ewing's/soft tissue sarcoma	100%	53%	45%	8%
Osteosarcoma	73%	45%	45%	7%
Central nervous system tumours	27%	20%	18%	3%
Germ cell tumours	55%	27%	45%	3%

* Responses from 11 centres in Australia and New Zealand (one returned survey left unanswered).
† Responses from 60 centres in North America (nine returned surveys left unanswered). ◆

questionnaire or pass it on to a more appropriate clinician within the centre. The completed surveys were then returned by facsimile. The survey was anonymous (questionnaires had no identifier), although if participants wanted to receive results of the survey, space was provided for them to identify themselves.

RESULTS

Twelve of the 13 centres (92%) completed and returned the questionnaire. Nine of these requested results of the study. In the previous North American study, 69 of 110 surveyed centres (63%) completed questionnaires.[6]

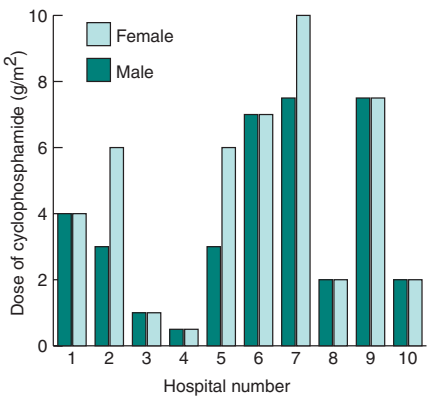
Existing practice

Sperm conservation: This was offered to postpubertal males in all centres (Box 2). Options for gamete collection included ejaculate (12 centres; 100%), epididymal aspirate (4 centres; 33%) and testicular biopsy (4 centres; 33%). Established links with a sperm collection and preservation service existed in 11 of the 12 centres (92%). Sperm preservation had been offered to males who had not completed sexual development in five centres (42%). Units were more likely to offer sperm preservation to males with lymphomas and sarcomas. This is probably partly a reflection of the age distribution of the disease incidences (Box 3). The total anticipated cumulative dose of the alkylator cyclophosphamide at which centres elected to offer fertility preservation in males varied from any at all to 7.5 g/m^2 (Box 4). Similarly, the total anticipated cumulative dose of radiation triggering discussion about sperm preservation ranged from any radiation up to 12 Gy for abdominal/pelvic sites, and from any radiation up to 24 Gy for spinal irradiation (Box 5).

Oocyte/ovarian tissue conservation: This had been offered to postpubertal females in 10 centres (83%). Options included ovarian freezing (eight centres; 67%) and ovarian transposition (five centres; 42%), with five centres having used both procedures. No centre had offered oocyte freezing or IVF and embryo freezing (the oldest patients were adolescents and none were in stable, mature relationships). One centre offering ovarian freezing did not have an established link with a fertility preservation service at the time. Five centres had offered fertility preservation to females who had not completed sexual development. Lymphomas, sarcomas and germ cell tumours were the tumour types for which centres most commonly offered oocyte preservation (Box 3). The total anticipated cumulative dose of the alkylator cyclophosphamide at which centres elected to offer fertility preservation to female patients varied from any to 10 g/m^2 (Box 4). Similarly, the total anticipated cumulative dose of radiation triggering a discussion of fertility preservation ranged from any radiation up to 12 Gy for abdominal/pelvic sites, and from any radiation up to 24 Gy for spinal irradiation (Box 5).

Counselling: Formal fertility counselling was offered in nine centres (75%). This was done by specialists in one of a wide range of disciplines and, in some centres, by more than one professional group. These included consultant physicians (oncologists, endocrinologists, obstetricians and gynaecologists, fertility specialists), nurses, fertility counsellors, social workers and psychologists. Of the nine centres that offered counselling, six had discussed sperm and oocyte preservation policies within the past 5 years. Formal counselling was not available in three centres offering sperm preservation, and one centre offering oocyte preservation.

4 Offer of sperm and oocyte conservation by cumulative cyclophosphamide dose*



* Responses from 10 centres (two surveys left unanswered). ◆

Guidelines: While 11 of the 12 centres (92%) felt that guidelines were needed, only one centre had them for both sperm and oocyte preservation, and one other for sperm preservation only.

DISCUSSION

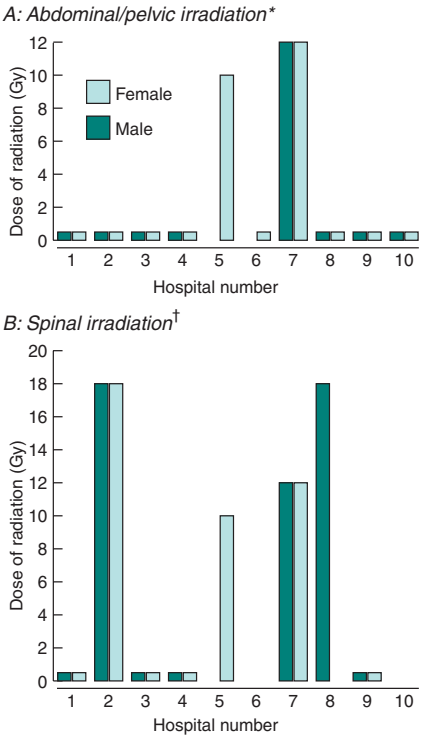
This is the first report of clinical practice with regard to sperm and oocyte preservation in children undergoing cancer treatment in ANZ. Given the high participation rate and the fact that over 90% of children (aged less than 15 years) newly diagnosed with cancer in ANZ are treated at one of the participating units,[7] the results are likely to be very accurate. However, not all treating oncologists were surveyed, and this may have influenced the results, particularly at the larger centres where individual physician preference may be a factor. A component of the variation observed may also be explained by some smaller units choosing to only offer less intensive treatments, and hence not requiring fertility preservation interventions. Despite these issues, the opportunity for discussion about fertility and access to services is inconsistent.

While the variation in practice is quite striking, it is considerably less than previously reported in North America in 2000.[6] In particular, all ANZ centres offered fertility preservation to postpubertal males, and a much larger proportion of centres are addressing the difficult issues of female fertility preservation. COG, the world's largest paediatric oncology collaboration, recently published long-term follow-up guidelines for survivors of child, adolescent and young-adult cancers, including a comprehensive review of the risk factors for infertility (http://www.childrensoncologygroup.org). The current recommendations for consideration of fertility preservation are for patients likely to receive a cumulative dose equivalence of:

- 7.5 g/m^2 cyclophosphamide;
- 1–3 Gy for abdominal/pelvic irradiation in males or 6–10 Gy in females; or
- 24 Gy for spinal irradiation

Although most ANZ centres are members of COG, no centre identified the COG guidelines as a source of guidance. In fact, many units had a lower threshold (any exposure) for offering fertility preservation than current evidence suggests is necessary.[8-11] Interestingly, despite data on the safety and efficacy of GnRH analogues in adolescents being very limited,[12] two centres were using such agents outside the setting of a clinical trial.

5 Offer of sperm and oocyte conservation by cumulative radiation dose



* Responses from 10 centres (two surveys left unanswered).

† Responses from 8 centres (four surveys left unanswered, including hospitals 6 and 10). ◆

Relatively fewer centres are undertaking fertility preservation procedures in patients who have not completed their sexual development. This is despite recent evidence that successful pregnancies have resulted from the use of sperm extracted from the epididymis or testis in pubertal males before the onset of first ejaculation.[13] On the other hand, collection of gametes in pre-ovulatory females has not led to subsequent restoration of fertility to date. However, several births have been reported after ovarian tissue grafting in women of reproductive age,[14,15] opening up difficult legal and ethical issues around the experimental nature of this procedure.

Overall, most centres are offering care consistent with best practice, with a fairly cautious and inclusive approach to the use of fertility preservation services for patients at risk. The lack of consensus probably reflects the historical lack of options, the lack of clear data on the true risk of infertility after exposure to certain toxic agents, and the ongoing uncertainty of the efficacy of certain treatment options. Experience with gametes and tissue from children and adolescents will undoubtedly expand in time. An improved understanding of the morbidity of infertility in survivors would also better inform the debate. In the meantime, the ethical question of the hazards and psychological distress caused by intervention versus the potential for future benefit remains a difficult one. Complicating any discussion is the potential conflict between a legal minor (the patient), who may not be in a position to assess the potential impact of infertility, and his or her parents. It is also important to acknowledge that, often, the urgency of commencing life-saving and potentially curative treatment must take precedence over any interventions aimed at preserving fertility.

Paediatric oncology units should provide a coordinated approach to discussion about cancer treatment and future fertility early in the course of treatment. The current uncertainty of future reproductive function for young people who have received chemotherapy or radiotherapy means that long-term follow-up and data collection must be instituted. As progress in reproductive technology continues at a great pace, clinicians must keep abreast of developments and make all relevant information available to families. Variations in practice in the setting of unresolved medical, legal and ethical issues suggest guidelines would be helpful.

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COMPETING INTERESTS

None identified.

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