PERSONAL PRACTICE

Fertility preservation for children treated for cancer (2): ethics of consent for gamete storage and experimentation

Institute of Child Health, University of Birmingham, Whittall Street, Birmingham B4 6NH, UK
R Grundy

Department of General Paediatric Medicine, The Royal London Hospital, Whitechapel, London E1 1BB, UK
V Larcher

Department of Obstetrics and Gynaecology, Division of Reproductive Biology, 687 Pine Avenue West, Montreal, QC Canada, H3A1A1, Canada
R G Gosden

Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK
M Hewitt
D Walker

Department of Haematology and Oncology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, UK
A Leiper

Department of Paediatric and Adolescent Endocrinology and Oncology, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK
H A Spoudeas

Department of Haematology and Oncology, Royal Hospital for Sick Children, 17 Millerfield Place, Edinburgh E19 1LF, UK
W H B Wallace

R Grundy, V Larcher, R G Gosden, M Hewitt, A Leiper, H A Spoudeas, D Walker, W H B Wallace

Infertility causes significant psychosocial morbidity by reducing both personal sense of well-being (health) and capacity to exercise self determination over reproduction (autonomy).¹ As the primary moral responsibilities of health professionals are restoration of health and respecting patients' autonomy, it follows that preserving fertility or treating infertility has sound ethical justification in adults. These arguments also apply to children. Children who develop cancer suffer misfortune; for this to be compounded by the burden of potentially treatable infertility seems doubly unjust. However, intervention to preserve fertility must have a sound evidence base as well as moral provenance. It should neither raise unrealistic expectations nor have long term adverse effects on the patient or their offspring.

Ethics of removal, storage, and manipulation of gonadal tissues

Preservation of fertility by assisted reproductive techniques (ART) is not an established part of cancer treatment for prepubescent children and without relevant research to determine its efficacy and safety it cannot be considered as such. Clinical research in adults is ethical if it is: (1) scientifically valid; (2) in the patient's best interest; (3) subject to individual ethical review; and (4) subject to informed consent.² Similar conditions apply to research in children with the additional proviso that alternatives are sought—such as animal models—before involving children.³ Physicians should have the necessary expertise and facilities to carry out the research.²

Surgical removal of gonadal tissue is of greater than negligible risk and minimal burden, so is justified only when combined with treatment intended to benefit the child concerned.³ As the benefit of storing gametes can be realised only in the future, it is important that removal of gonadal tissue is considered as part of an ongoing process rather than a discrete event. Although harvesting gonadal tissue may be of high risk if taken in isolation, within the context of the child's illness it may pose minimal additional risk,^{3 4} especially if combined with a diagnostic or

therapeutic procedure which requires anaesthesia. Risk assessment is difficult in the absence of data; for example, the risk of retransmission of malignant cells or of passing on a genetic susceptibility to malignant disease in future generations is unknown (see part 1 of this article⁵). Furthermore, the likelihood of generating gametes and successfully implanting embryos is currently unquantifiable. Additional risks to future progeny may not be foreseeable and will only reveal themselves over time. Despite this, we believe it is neither possible nor desirable to place limits on research which have unquantifiable benefits.⁶

Valid consent is necessary for clinical research; it renders potentially harmful interventions both ethical and legal. To be valid, consent must be informed, voluntarily obtained, and given by a competent person. In practice, it may be difficult to satisfy these criteria, especially in cancer treatment.⁷ The information necessary for parents and children to make an informed choice about fertility preservation by gonadal tissue storage is arguably at least that which a reasonable person would want in similar circumstances.

This reinforces the need for consent taking to be a dynamic process and emphasises the obligation for researchers to relay further information to families which may arise from research. Alternative treatments to preserve fertility should be disclosed as should the option of no treatment, instead of relying on future advances in reproductive medicine to maximise an individual's residual reproductive capacity.

Such information is inevitably complex and its comprehension cannot be guaranteed. Legal competence to consent requires that the individual giving it is able to understand the information given, believes that it applies to them, retains it, and uses it to make an informed choice. Parental anxieties about their child's illness and prognosis may reduce their competence. It may involve consideration of a future which neither they, nor their child, can envisage or have discussed, for example, whether the child would wish to have children in the future. Therapeutic imperatives may

Correspondence to:
Dr Grundy
r.g.grundy@bham.ac.uk

Accepted 21 November 2000

limit the time available for discussion, which in turn imposes constraints on the voluntariness of the consent.

Some of these practical difficulties may be alleviated if obtaining consent is considered as a continuum which can be divided into several stages. A two stage consenting process has already been advocated for the use of human tissue for research purposes.⁶ First stage consent could be obtained for gonadal harvesting and storage and the second stage might involve manipulating the tissue to form gametes at a later date.

Such an approach could be tailored to overcoming some of the difficulties inherent in deciding who owns the tissue being removed. In other research involving human tissue it has been suggested that the tissue should be considered as a donation on which conditions may be set and in which the donor transfers his or her rights of usage to an appropriate custodian. This may be satisfactory for tissue over which a donor has no future claims, but it may not be appropriate for gonadal tissue where the intention is to use it for the donor's future benefit. In these circumstances it may be best to consider the tissue as a loan which may be recalled in the future and over which the storing authority has stewardship. The terms and conditions of the loan may form the basis of consent which could include what might be done with the tissue should the child die.

The two stage consent process may have other practical advantages. Tissue needs to be harvested and stored before a child is able to express wishes and preferences of their own, including whether they are likely to want future offspring. Many children in whom harvesting is an option lack the capacity to understand the nature and purpose of what is proposed.⁸ They may also lack sufficient capacity to assent to the research proposal.⁹ This does not obviate the need to inform and involve them commensurate with their ability, experience, and understanding. The duties of relevant professionals and parents of children who are not Gillick competent and lack capacity to assent is to act within the child's best interests. (In English law the validity of a child's consent to medical treatment depends on their capacity or competence to do so. Under the Family Law Reform Act (1969), children over 16 years can consent to medical treatment, provided that they are not incompetent. Children under the age of 16 may consent to treatment if they have sufficient understanding and intelligence to enable them to understand fully what is proposed. A child who can show this ability is referred to as "Gillick competent" after the legal case in which judgement was given.⁸) Clinicians have a responsibility to offer treatment which is in accordance with the standards of a reasonable and competent body of medical opinion and which should be evidence based. Parents can consent to clinical research on their child which attempts to define the evidence base for fertility treatment, provided that certain safeguards are met.^{2,3}

Regulation of use of tissue, licensing, ethical approval, and gaining consent

Regulation provides a means of societal control of technologies which may have wide ranging social implications. For example, in the UK, harvesting, storage, and manipulation of mature gametes from human subjects and experimentation on the embryos they produce is subject to legal constraints embodied in the Human Fertilisation and Embryology Act.¹⁰ Implementation of the act is overseen by the Human Fertilisation and Embryology Authority (HFEA) which grants licences to individuals for certain procedures involving gametes. The act specifically excludes proxy consent for harvesting, storage, experimentation, or use of gametes for fertilisation.¹⁰ For those who are under 18 years of age, it states explicitly that valid consent must be obtained before gametes are harvested. The HFEA has stated that "it is legally impossible for anyone to give consent for storage of gametes on behalf of another. Thus people with parental responsibility cannot give consent on behalf of the child".¹⁰ In response to media reporting of storage of gonadal tissue from children and correspondence in the medical press,^{11,12} HFEA has clarified definitions including what constitutes a gamete. It defines a gamete as "a cell with a haploid set of chromosomes which is able to take part in fertilisation with another of the opposite sex to form a zygote". This was further refined for boys with reference to pubertal stage, suggesting that a licence to harvest would be required if a boy had reached Tanner stage II or beyond.^{13,14}

This means that for some, but not all children, harvesting and storage of immature germ cells can take place without licence, provided that parents give valid consent and that the procedure is in the child's best interest.¹³ Risks associated with storage include cross contamination during storage, the hazards of growing eggs in vitro, and of experimentation with immature germ cells. The HFEA recommendations were understandably not designed with children or cancer patients in mind, nor did they foresee the rapid advances occurring in ART.

The code of practice proposed by the Polkinghorne Committee for the use of and research on fetuses and fetal tissues suggests guidelines which could equally well apply to the removal and storage of gonadal tissue from prepubertal children.¹⁵ For example, the process of harvesting, storage, and manipulation should be described in a protocol, examined by an ethics committee, and be subject to review until the validity of the procedures can be recognised as part of routine medical practice. An ethics committee would have specific duties to examine the process of research, have access to records, and confirm that the tissue is being used for the purpose stated in the protocol. The whole process could be protected by a series of consents which would set limits on the use of gonadal tissue, similar to those currently required for adults by the Human Fertilisation and Embryology Act.

Table 1 Development strategy for research into germ cell harvest and storage

Phase 1
Develop a consensus of treatment related risks of germ cell damage
Develop a consensus of risks to the child associated with germ cell harvest
Phase 2
Develop methods of prospective data collection aimed at registering germ cell tissues, collection methods, and conditions of storage
Develop a register of patients at risk of subfertility
Phase 3
Monitor success rates of the use of stored germ cell material and the fertility rates of all those registered
Phase 4
Careful follow up of the offspring of children born following assisted reproduction

In the UK, paediatric oncologists routinely obtain valid consent for therapeutic research in over 80% of their patients. This would seem to be a relevant precedent for obtaining proxy consent to germ cell harvest and storage as well as experimentation concerning storage and maturation if such a process were approved by a relevant ethics committee. Indeed, with the current state of knowledge it would seem an essential requirement for ethically acceptable clinical and research practice.

Recommendations

To enable the best advice and care for children undergoing cancer treatment and their parents, the following issues are of importance.

- Well designed, performed, and documented research with rapid dissemination of results
- Developing the process of gaining informed consent for germ cell harvest storage and experimentation
- Rigorous review of procedures and evaluation of results obtained
- Multidisciplinary work, both in research and in the care of the child
- Continuing multidisciplinary dialogue and the exchange of experience and expertise
- Developing new areas of expertise, such as the removal of reproductive tissue from children
- Collection of information on a long term basis, involving follow up of patients, with eventual central collection of data
- Maintenance of high standards in the collection and storage of tissue and record keeping
- Agreement on a voluntary code of practice governing all aspects of germ cell work
- Work in this experimental area should be conducted in a limited number of centres.

The experimental nature of this work makes it essential to ensure that clinical and research practice develops in a phased and coordinated manner, as outlined in table 1.

Conclusion

Although the primary objective of modern multimodality treatment of childhood cancer is cure, it is axiomatic that the quality and cost of such treatment should be fully considered with patients and/or their guardians. The effect of treatment on subsequent fertility is an important factor, given the known adverse psychosocial impact of infertility. However, assuming that the child's best interests remain paramount, then the experimental uncertainties and ethical issues of gonadal preservation need to be clarified further. In offering the chance of preserving fertility to parents of young children, we are inevitably raising expectations. Therefore clinicians bear a responsibility to counsel families cautiously with respect to success rates in the future, the potential for harm, and concerns over circumventing the natural barriers to selection. The significant ethical and consent issues raised by the new technologies of ART deserve wide consideration.

- 1 Doyal L. *Infertility counselling for IVF: the moral and legal background*. Oxford: Blackwell, 1995.
- 2 Royal College of Physicians. *Guidelines on the practice of ethics committees in medical research involving human subjects*. London: Royal College of Physicians, 1996.
- 3 Royal College of Paediatrics and Child Health Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2000;**82**:177–82.
- 4 Nicholson RH. *Medical research with children: ethics law and practice*. Oxford: Oxford University Press, 1986.
- 5 Grundy RG, Gosden RG, Hewitt M, et al. Fertility preservation for children treated for cancer (1): scientific advances and research dilemmas. *Arch Dis Child* 2001;**84**:355–9.
- 6 Nuffield Council on Bioethics. *Human tissues; ethical and legal issues*. London: Nuffield Council on Bioethics, 1995.
- 7 Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. *BMJ* 1993;**307**:1199–201.
- 8 Gillick v West Norfolk and Wisbech Area Authority. 1985;3 AU ER402.
- 9 Hondrusek N, Abramovitch R, Pencharz P, Koren G. Empirical examination of the ability of children to consent to clinical research. *J Med Ethics* 1998;**24**:158–65.
- 10 The Human Fertilisation and Embryology Act. London: HMSO, 1990.
- 11 Hewitt M, Walker DA, Sokal M. Human Fertility and Embryology Act 1990 discriminates against children. *BMJ* 1998;**316**:1094.
- 12 Deech R. Human Fertility and Embryology Act 1990 discriminates against children. *BMJ* 1998;**316**:1095.
- 13 Department of Health. *Storage of testicular tissue*. Report no. 17:2. London: Department of Health, 1997.
- 14 Tanner JM. *Fetus into man: physical growth from conception to maturity*. Castlemead, 1989.
- 15 Human Embryology and Fertilisation Authority. *Codes of practice*. London: HEFA, 1993.