A STRATEGY FOR

FERTILITY SERVICES

FOR SURVIVORS OF CHILDHOOD CANCER

by a
Multidisciplinary WORKING GROUP
convened by the

BRITISH FERTILITY SOCIETY

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Executive Summary

Children being treated for cancer are increasingly likely to survive and many will grow to maturity. A significant number of these (15%) will have compromised reproductive function as a result of their cancer treatment. These numbers will increase so that impaired reproductive function becomes a significant public health problem for the future. Progress in long term ovarian tissue (cryo)preservation has led to the possibility, after they reach adulthood, of using gametes obtained from these children prior to treatment. This Report describes issues that need to be addressed.

Gonadal tissue preservation by freezing (cryopreservation) is still an experimental procedure and research is required to establish the appropriate procedures and risk-benefit profile. There is no Health Service provision for tissue retrieval or storage. Organisation of future clinical care of candidates who wish to use their stored tissues will require multidisciplinary input. The relative risks and benefits of gonadal tissue retrieval and preservation have not been established. Uncertainty about technical procedures should be resolved by research protocols, which should be submitted to the appropriate research ethics committee. In contrast sperm storage for post-pubertal boys is a well established and proven technique which should now be considered routine.

Psychosocial aspects of childhood cancer management are important and need to be dealt with by personnel appropriately experienced in psychology, paediatrics, oncology and reproductive medicine. Psychosocial support also needs to be accessible to survivors long after the successful completion of their cancer treatment.

Meticulous documentation is required for adequate follow-up of all aspects of the oncology management. The processes of obtaining tissue for conservation, the cryopreservation technique and conditions of storage also need to be documented in a standard manner. The most efficient way of optimising all regimes for outcome of the cancer treatment and subsequent conception is by longitudinal and prospective data collection and review of the retained records of the various treatment details and these also need to be accessible for long term follow up.

The Dept of Health has produced a Code of Practice for Tissue Banks. Paediatric Oncology and Assisted Conception Units will need to comply with these regulations by April, 2003. Only in this way can tissue containing immature gametes be used in the NHS in future. Liaison with a certified Tissue Bank may facilitate development of accreditable procedures for collection, transport and storage of tissue.

A series of recommendations has been made to facilitate the development of a multidisciplinary service for these children and adults they will eventually become. They are directed at responsible organisations and individual units as well as the various arms of government. Appropriate responses will collectively ensure an effective outcome, which is the establishment of a properly funded, ethically sound and scientifically based service.

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BACKGROUND

Each year about 120 per million children in Britain suffer from cancer. Since the registration of children's cancer centres in 1977 (22 UKCCSG[1] centres) multicentre protocols have dramatically increased overall survival to 60-65%. It is estimated that currently 1 in 1000 young adults (25-35 years) have survived childhood cancer. However, the aggressive therapy required for cure may have longer term psychosocial and health-related consequences: impaired hormonal responses and future infertility. The extent of this infertility is unclear for three reasons: first, new cancer therapies are constantly developing; second, survival (and hence potential reproductive recovery) is further prolonged ; and third, new techniques have been developed in reproductive science. One of these, intracytoplasmic sperm injection (ICSI), has rapidly become established. Another, cryopreservation of immature oocytes and autotransplantation has been successful in sheep, leading to the birth of viable young. In the human, cryopreservation has been attempted and further application shows potential. Moreover, its promise of revolutionizing future fertility prospects for these children and young people, whose own fertility may be long in the future, is inspirational.

In 1998 the Joint Council for Clinical Oncology of the Royal College of Physicians published a Working Party Report on the Management of gonadal toxicity resulting from the treatment of adult cancer. The idea behind the current Working Group arose during a meeting in Cambridge on "Ethical and Research Dilemmas for Children treated for Cancer" in December, 1999. In January 2000 the Royal College of Obstetricians and Gynaecologists published the Report of a Working Party on the Storage of ovarian and prepubertal testicular tissue. In August 2000 the British Fertility Society published their recommendations for Good Practice on the Storage of ovarian and prepubertal testicular tisse (Nugent et al., 2000). This was followed by symposia on the topic at the Teenage Cancer Trust Conference at the Royal College of Physicians in April, 2001 and the annual British Society of Paediatric Endocrinology meeting at Sheffield Hallam University in September, 2001. In October, 2001 the Royal College of Obstetricians and Gynaecologists held a meeting on Reproductive health services following childhood cancer.

From all of these discussions it was evident that although paediatric oncologists had developed sophisticated management programmes, the children would either continue to be seen by their paediatric practitioners (who may be less aware of reproductive options) as adults or be passed on to practitioners of adult medicine who were ill prepared for the problems generated by these complex treatments. This applied particularly to the future management of their fertility, which could show any degree of compromise and at many different points of the hypothalamo-pituitary-target gland axis. There has also been considerable activity in adults taking ovarian samples for cryopreservation in an attempt to safeguard future fertility. That action was based on limited animal data, without the necessary understanding of how to reach the long term objective of achieving pregnancy in the human. Further, the support systems required for this sequence of events had not been defined.

The British Fertility Society convened this multidisciplinary Working Group to define a strategy for developing reproductive health services for these survivors. It is grateful to the participants who responded so enthusiastically and embarked on a journey of exploration and mutual education. The members of the Working Group are listed in Appendix IV with their affiliations and areas of expertise. The Group met on seven occasions between December 2000 and January 2002.

The Report describes current approaches to the treatment of childhood cancer. A protocol is laid out for creating a record that will be valuable for future fertility management. This is followed by discussion of the psychosocial, ethical and legal aspects (further elaborated in Appendix. II). The issues in children are more complex than in adults and there is a clear need for separate discussion of the immediate curative treatment events and those directed at conservation of future fertility potential after effective treatment.

Recent government regulations on tissue cryopreservation have tightened storage procedures for immature gametes/tissue. These are reviewed and will need to be considered carefully by Assisted Conception Units. The current approaches to management of fertility in those who do and those who do not have gametes or tissue cryopreserved are described.

Finally, the framework for cancer care in the National Health Service has changed markedly and this is briefly described.

Those practising in paediatrics need to be aware of progress in reproductive medicine and assisted conception in particular. Those working in secondary and tertiary level fertility units need to be aware of the major advances in paediatric oncology and the nature of the potentially compromised fertility of their newly adult patients. There needs to be considerable sensitivity to the psychosocial consequences in these young people, who should be regarded as having a chronic illness, rather than entirely "cured" or free of disease. Similar issues are raised in the fertility management of adults with cancer, those having gonadotoxic therapy for other conditions or those likely to experience an early menopause for genetic or other reasons. The latter two problems may usefully also be considered in a similar manner.

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FERTILITY PRESERVATION IN CHILDHOOD CANCER CARE

Summary

Progress in long term reproductive tissue preservation has led to the using gametes obtained from children prior to treatment, when they reach adulthood. Research into improving methods of tissue preservation is required. Issues of consent, long term record maintenance, multidisciplinary communication and funding need to be resolved. There needs to be extensive documentation, so that on the long term, fertility treatment can be optimised. The data can be used for research to improve outcome and better understand the consequences of cancer treatment. This chapter reviews the details that should be considered in trying to achieve these objectives.

Children treated for cancer are increasingly likely to survive: the overall chance of cure is 65% and for specific cancers e.g. leukaemias lymphomas and germ cell tumours, nearly 100%. A significant number of survivors has grown to maturity, each having an average of a further 68 years of life ahead, compared to 10 years for each adult cancer patient; some even have offspring. Some 15% will have a high risk (95%) of early and irreversible gonadal failure, while others may have lesser degrees of compromised reproductive capacity as a result of their cancer treatment (Wallace et al., 2001). Different cancers are associated with different risks of future fertility compromise and these may be classified as shown in Table 1. Those most at risk are often those most intensively treated with consequent multiple toxicities (for example those requiring a Bone Marrow Transplant, BMT). Nevertheless survival is still increasing - BMT survival is up to 60% - so that impaired quality of life and reproductive function become a significant concern. Males are more susceptible to subfertility following chemotherapy than females, but females may be at risk of premature menopause.
Treatment with some chemotherapeutic agents is particularly likely to result in gonadal toxicity. Those most likely to cause germ cell damage are shown in Table 2. These are toxic agents, including alkylating agents, specifically cyclophosphamide, procarbazine and cis-platinum, lomustine/carmustine (proven dose-dependent toxicity)

Conditions other than cancer which may be treated by chronic, lower dose administration of cytotoxic drugs. Children and young people suffering from these **non-cancerous** conditions may also be potentially at risk of gonadal damage and be suitable for fertility conserving measures.

The new challenge facing professionals in many different disciplines is how the child's wellbeing can be protected at a time when curative treatments to avert mortality are juxtaposed with options for protecting fertility. New and competing issues and options are raised for the child and the family to consider. There are already a number of options for managing potential fertility problems:

there may be natural restoration of the individual's fertility over time in the male (Meistrich et al.,1989).

attempts may be made to protect or initiate restoration of reproductive function by the use of hormonal or other treatment before or after gonadotoxic chemotherapy.

harvested and cryopreserved gametes may be used in the future, already used for many years for the adult male, but not yet efficiently for the female.

germ cells and tissues containing immature gametes may be collected, stored and manipulated with the ultimate aim of enabling an individual to become a parent of a genetically related child;

this has only so far been successful in animal models

Except in the case of the post-pubertal and competent male[1], where sperm banking prior to therapy is recommended, there is uncertainty over the most effective methods of attempting to maintain or restore an individual's fertility, each other method being experimental with unknown efficiency and potential advantages, disadvantages and risks. Where there is uncertainty amongst professionals, there are

[1] **General Medical Council (1998) Seeking patients' consent: the ethical considerations, describes Gillick competence**

particular difficulties in advising patients and parents on what is likely to be the most appropriate course of action. There are special concerns in relation to the treatment of children because of the need to consider the extent to which they are able and/or wish to participate in decision making. The importance of involving children in discussion and giving them the support they need to play a meaningful role in treatment decisions is well recognised, by both professional (Royal College of Paediatrics and Child Health) and legal (Children Act, 1989; UN Convention on Rights of the Child, 1990) bodies, although there is a need to consider carefully how this may best be achieved. However, there will be cases where decisions are made on the child's behalf, raising problems of deciding what is likely to be in the child's best interests both in the short and the long term, particularly where the issue at stake is a quality of life rather than quantity of life choice and the nature of the intervention an experiment governed by separate ethical constraints (Declaration of Helsinki, Edinburgh, 2000).

Table 1 Risk of future fertility compromise associated with different cancers

Low	Medium	High
Acute lymphatic leukaemia	Acute myeloid leukaemia	Total body irradiation
Soft tissue sarcoma Stage I	Wilms' tumour	Localised radiotherapy:
Germ cell tumours with	Hepatoblastoma	pelvic or testicular
gonadal preservation and	Osteosarcoma	High dose chemotherapy
no radiotherapy	Soft tissue sarcoma >Stage I	"conditioning" for bone marrow/
Brain tumour	Neuroblastoma	stem cell transplant
surgery only	Non-Hodgkin's lymphoma	Hodgkin's disease: alkylating
cranial irradiation	Hodgkin's disease:	agent-based therapy (males)
	"hybrid therapy"	Ewing's sarcoma (suspected)
	alkylators only (females)	Soft tissue sarcoma: metastatic
	Brain tumour:	
	craniospinal radiotherapy +/-	
	chemotherapy	
	cranial irradiation (>24 Gy)	

Notes:

1 There is insufficient evidence to be definitive, so this represents the best educated guide.
2 This Table may be used as a guideline on which to base fertility counselling at the onset of treatment relating specifically to gonadotoxicity.

The development of strategies for minimising the effects of cancer treatment on future fertility is still at an early stage. Some interventions under consideration can proceed within already established frameworks designed to deal with some of the issues: e.g. the storage and use of mature gametes is regulated in the United Kingdom by the Human Fertilisation and Embryology Authority (HFEA). However such a regulatory authority was not designed with children in mind. There may therefore be a need for reappraisal and perhaps amendment of this framework to offer children the same opportunity and protection as adults.

Other types of intervention, such as the storage and use of germ cells and tissue, currently fall outside the remit of the HFEA, because they are considered not to be or contain mature gametes. Since these techniques are at a preliminary stage of development we consider that they should be governed by the principles applicable to research unless or until there is proven therapeutic benefit. Tissue stored for possible therapeutic use will be controlled by regulated tissue banks, whereas tissues stored for research fall outside those regulations. If it is intended in the future to return such tissue, or oocytes derived from it, to the body, it should be stored in compliance with the relevant regulatory regime.

In enabling the best advice and care to be given to children embarking on cancer treatment and their parents we consider that the following issues are of crucial importance:

rigorous review of procedures and evaluation of results obtained.

multidisciplinary work both in the care of the child and in research.

continuing multidisciplinary dialogue and the exchange of experience and expertise.

collection of information on a long term basis – involving follow-up of patients with the agreement of the patient and family and perhaps central collection of data.

the maintenance of high standards in the collection and storage of tissue and record keeping.

well-designed, performed and documented research with rapid dissemination of results.

In the aim of successful germ cell storage, pretreatment consideration of germ cell harvest and storage is in the best interests of the child.

Table 2 Gonadotoxicity of Chemotherapeutic Agents

Group	Proven Gonadotoxicity
Alkylating agents	Cyclophosphamide
	Chlorambucil
	Melphalan
	Busulfan
	Carmustine
	Lomustine
	Mechlorethamine
	Procarbazine
	Cisplatin
Vinca alkaloids	Vinblastine
Antimetabolites	Cytosine arabinoside

We recommend that clinical and research practice in this area develop in a phased manner:

38 Develop a consensus of treatment-related risks of germ cell damage.

39 Develop a consensus of risks to the child associated with methods of germ cell harvest.

40 Develop methods of prospective data collection aimed at registering germ cell tissues stored, collection methods and conditions of storage. In addition, a register of patients at risk of sub-fertility (including those who choose not to undergo harvesting procedures) should be established.

41 Monitor success rates for the use of stored germ cell material, fertility rates of all those registered and organise the follow-up of any offspring.

There are many aspects of management that need to be considered in treating childhood malignancy. Keeping in mind the patient's long term fertility prospects requires attention to many details prior to the commencement of any therapy. The response will be determined by the patient's maturity, hence ability to consent. Arrangements for gamete storage are now complex and meticulous documentation[2] is essential. These records will be the basis of management in a Late Effects Clinic following successful therapy and subsequently in an Assisted Conception Unit. Careful liaison with the centre storing any germ cells or gametes (Assisted Conception Unit or Tissue Bank) will need to be established.

[2] Long term record storage will be required for follow up and research. However the issue of informed consent and cancer registries has not yet been resolved. The Health and Social Care Act, Section 60, established in August, 2001 a Patient Information Advisory Group (Statutory Instrument 2001/2836), which will consider what data can be used for cancer registration without informed consent. The recommendations of this group will be relevant and significant.

FEMALES

Retrieval, cryopreservation and storage procedures could be considered in young children who have potentially more ovarian follicles to harvest. However, the operation is also potentially more hazardous, possibly requiring laparotomy rather than laparoscopy, and removal of a relatively larger amount of ovarian tissue.. The smallest children have a larger ovarian pool of oocytes and are those who are most likely spontaneously (perhaps temporarily) to resume cyclical ovarian function.

In view of this and the wider ethical debate, tissue cryopreservation is not currently recommended as routine for these children; it remains a research procedure. Specific research studies in this area should be carefully reviewed by the appropriate ethical committee, which should be fully informed of the complex debate and have recourse to appropriate legal advice. Specific guidance should be requested on tissue storage and experimentation. Parents/families who specifically request information on this issue should have these principles explained.

Psychosocial support should be offered for their discussions about fertility preservation. These youngsters may be recognised as "Gillick competent" if sufficient time and explanation are given. If their gonads may be capable of producing mature gametes, ovarian stimulation and oocyte collection may be considered in post-pubertal females although at present mature oocyte storage and subsequent use has limited success. Although these procedures are established, they may be inappropriate because of the length and intensity of a stimulated cycle and its associated risks. Alternatively, cryopreservation of samples of the ovarian cortex could be considered.

General **Inclusion Criteria for offering Gonadal Tissue Cryopreservation**
The chance of survival, the risk of subfertility and the age of the patient need to be taken into account. However, the following categories should be included:
38 those having high dose therapy involving alkylating agents or total body irradiation (TBI).
39 those having direct pelvic irradiation.
40 those having cycles of MOPP/CHOPP for Hodgkin's disease.
41 those who are Gillick competent
42 those who are HIV and Hepatitis B and C negative

General **Exclusion Criteria for offering Gonadal Tissue Cryopreservation**
All subjects:
38 having an excessive surgical risk such as a bleeding diathesis
39 who are not Gillick competent (unless their parents can consent to storage of tissue in the child's best interest).
40 having primary or secondary ovarian malignancy, except where the ovaries are being removed anyway, the risk being less than that of two separate procedures. This tissue could possibly be used in the future for *in vitro* follicle culture
41 the procedure would cause excessive delay in curative treatment

Decisions should be **individualised** when:
38 there is a known familial genetic predisposition to disease
39 the patient is a carrier of viral infection (HIV, Hepatitis B or Hepatitis C) as separate storage facilities are required.

Psychosocial support should comprise:
1 independent counselling by practitioner(s) with paediatric, endocrinological, reproductive medicine, psychological, mental health or combined experience in assessing competence and knowledge of the issues.
2 Information, separate from that provided by the oncologist and preferably given over several days.
3 written information that has been externally reviewed and also piloted.
4 some assessment and statement of competence.

Seeking Consent

There should be structured interviews and the consent should involve if possible a trained psychosocial specialist, paediatric oncologist and reproductive medicine specialist/scientist in establishing competence and understanding.

If appropriate, this could include:
42 written consent to obtain germ cell tissue in the female
43 written consent to cryopreserve the germ cells or mature gametes, as required by the HFE Act, 1990.
44 written consent to dispose of the tissue in the event of death or incapacitation.

Without research on tissue obtained in this way there will be no information available on which to base future management. Lack of research increases the risk of failure when there is a need to use the tissue for future fertility. After cryopreservation of a tissue sample, up to 10% of it could be thawed for histological examination to determine whether the frozen tissue is likely to be in a satisfactory condition for future use by the patient. Such confirmation would indicate good practice and would be a sound basis on which to base counselling. The thawed tissue could be used for research. It would be helpful to try and obtain:

a written agreement to offer part of the tissue obtained for research.

a written agreement to donate the tissue for research in the event of death.

a statement of understanding of the experimental nature of the procedures and their potential hazards.

an acceptance of the need to be screened for HIV, Hepatitis B and C.

a statement that consent to treatment cannot be given at that time and that separate written consent may be obtained from the individual at a later date after proper counselling in an Assisted Conception Unit.

a statement that future NHS or private fertility treatment is not assured.

parents/supervising medical staff/G.P.s should be asked to inform the laboratory in the event of death of the patient.

Prior to gonadotoxic treatment the patient should undergo:

recording of height, weight and body mass index (BMI).

pelvic/vaginal ultrasound for ovarian volume, activity/cycle timing and uterine dimensions,

serum sampling for LH, FSH, progesterone, oestradiol, testosterone, inhibin and thyroid function tests (cycle timed when appropriate),

HIV, Hepatitis B and Hepatitis C screening
laparoscopic surgery for ovarian biopsies or removal of a single whole ovary (to prepare ovarian cortical slices for cryopreservation) according to predetermined criteria *before* chemotherapy or radiotherapy is administered.

After treatment
There should be a record of:

the decision and clinical outcome in all patients counselled

any data on the quality of germ cell tissue sample and gametes obtained

any peri-operative complications of tissue retrieval.

counselling given.

the time taken from counselling to tissue retrieval.

Further,
1 regular contact with the storage facility should be maintained.
2 a register of paediatric patients, with appropriate consent, should be initiated through UKCCSG.
3 endocrine assessments should be made in collaboration with the Late Effects Clinic and later with an Assisted Conception unit.

All female patients, when able to understand the implications, and including existing adult survivors of childhood cancers, should be advised of the potential for:

spontaneous pregnancy, and possible complications e.g miscarriages/premature birth following uterine irradiation.

considering oocyte or embryo cryopreservation as a precaution against an early menopause, recognising the difficulties with this procedure.

likely good health of any children born (although follow up is still short).

access to oocyte donation programmes

surrogacy, if uterine function is affected.

being referred to an NHS fertility clinic for assessment / advice.

side effects of cancer treatment (eg cardiotoxicity/renal problems) that may impact on pregnancy.

psychotherapeutic support in developing peer relationships etc.

MALES

38 Sperm banking should be offered to post-pubertal males (if consent can be given under the terms of the 1990 Act) regardless of diagnosis and treatment.

39 Currently no surgical procedure for germ cell retrieval is established or recommended in pre-pubertal males *(testicular biopsy is feasible for adults)*

40 Any studies in this area need careful consideration and independent approval by an appropriate research ethics committee.

41 Alternative gonadal protection strategies are currently being explored in primates.

42 Psychosocial support should be offered for their discussions about fertility preservation. If a boy is Gillick competent he should be offered the opportunity to produce a semen sample. If he is non-competent, it is inappropriate to approach him under the HFE Act; as without written informed consent, the sperm cannot be stored.

A leaflet should be given in advance of counselling (see Appendix III).

Independent counselling should be given by a dedicated clinical nurse/practitioner with reproductive medicine experience. There may be a need to teach masturbation.

1 It is desirable to obtain several pretreatment donations. The date and result of semen analyses must be clearly recorded in the medical notes. Although in the past, discussion and donations have been made over several days whilst commencing cancer treatment, there is evidence in rats that treatment is associated with sperm DNA damage, stress response gene expression in the testis, embryo loss, fetal malformations and second generation effects (Qiu, Hales and Robaire,1992). These effects suggest that sperm banking should be completed prior to commencing anti-cancer treatment. Even apparently poor samples may later be suitable for intracytoplasmic injection (ICSI).

If a semen sample cannot be obtained, electroejaculation under anaesthesia may be offered as an alternative to testicular biopsy.

Prior to biopsy, there may be benefit in performing a baseline ultrasound examination of the testes as scars may later be evident. As there are anxieties about the increasing rate of testicular cancer in young men, an ultrasound image taken prior to a biopsy may help in interpreting later images.

Psychosocial support should comprise:

independent counselling by practitioner(s) with paediatric, endocrinological, reproductive medicine, psychological, mental health or combined experience in assessing competence and knowledge of the issues.

information separate from that provided by the oncologist and preferably given over several days.

written information that has been externally reviewed and also piloted.

some assessment and statement of competence.

giving a leaflet explaining sperm donation (see Appendix III) followed by discussion and checking understanding.

The patient should **understand*:***

that he has sole responsibility for making all decisions about fertility preservation.

it is voluntary and he can decline.

it is confidential (parents need not know of any donations).

what happens if he "fails" to produce a semen sample and the reasons for failure.

the estimated chance of infertility.

that he is not consenting to future treatment at this stage.

potential for future fertility treatment for his partner including intracytoplasmic sperm injection (ICSI).

the difference between potency (which is usually preserved) and infertility.

the consent forms.

Seeking Consent

There should be structured interviews and the consent should involve a trained psychosocial specialist, paediatric endocrinologist/oncologist and reproductive medicine specialist/scientist in establishing competence and understanding (consistent with the HFE Act, 1990).
If appropriate, this could include:

written consent to storage : HFEA forms should be used [HFEA(006)].

written consent to the use of part of the sample for research, if appropriate and freely given.

written consent to disclosure of the sample quality to the referring practitioner.

written consent to disposal on death or incapacitation.

written consent to donation for research, if appropriate,

a written statement that storage of gametes does not mean that future NHS or private treatment can be assured.

Prior to treatment

Males should undergo:
40 pubertal assessment with recording of height and weight.
41 serum sampling for LH, FSH, testosterone and inhibin.
42 recording of the diagnosis and stage of disease.
43 recording of potentially gonadotoxic treatment to date (cumulative dose).

After treatment:

5 the follow-up record should have the outcome and cumulative total doses of gonadotoxic treatments updated.
6 the patient should be offered a chance to donate semen for analysis and banking if specimens have not previously been stored.
7 if sperm samples have not been stored prior to treatment, he should be encouraged to provide samples beginning at least 3 months after the conclusion of treatment to reduce the risk of storing damaged sperm.
8 he should be advised about the possible need for ICSI. If he requires fertility advice or is seeking fertility treatment he should be referred to an Assisted Conception unit for discussion.

Conclusions

1 Children being treated for childhood cancer are increasingly likely to survive.
2 The development of gonadal tissue cryopreservation creates the opportunity to elaborate long term strategies.
3 Systems must be established to foster progress from the presentation of the child with cancer through counselling, with or without cryopreservation of the gonadal tissue, to spontaneous or assisted conception.
4 The initial clinical details including endocrine status should be documented.
5 The issues that the subject understands need to be identified and recorded.

6 All written information should be appropriately reviewed and piloted.
7 The provision of written explanatory material should be documented.
8 The fact that psychosocial support has been provided, independent of those providing the oncological treatment, should be recorded.
9 Whether a child is Gillick competent or incompetent must be recorded.
10 Consent for storage of tissue and any consent for its use in research, each after appropriate discussion, should be recorded on specifically designed forms.
11 The decisions about disposal of tissue or its use for research, in the event of death, should be recorded.
12 The need for research should be recognised at all points.
13 There should be prospective medical and mental health research at all stages, so that outcome may ultimately be optimised.
14 Oncology Units need to develop links with Assisted Conception Units.
15 Legal aspects of consent for ultimate use of the stored samples need to be developed (cf Chapter 8).
16 The Tissue Banks Code of Practice regulations must be complied with by all Units (cf Chapter 5).
17 Patient commitment and the intense multidisciplinary nature of treatment should be recognised.
18 There are implications for long term health surveillance of patients and their offspring as well as recording data on interventions.
19 Treated women should be followed up at least to their menopause.
20 All offspring should be followed up long term.

Recommendations

Oncology Units should ensure that:

1 all competent males who can produce semen have the opportunity of discussing the preservation of their fertility with an appropriately trained person.
2 all competent females have the opportunity of discussing the preservation of their fertility by conservation of a sample of gonadal tissue or oocytes with an appropriately trained person prior to gonadotoxic therapy or removal of ovarian tissue.
3 the parents of non-competent children are given the opportunity of discussing the issues relating to their children's gonadal tissue conservation and agreeing an appropriate course of action.
4 in addition to obtaining consent for gonadal tissue conservation, where appropriate, the rationale and need for relevant research should be explained. An attempt should be made to seek consent to use a part of the tissue for research, but participation in the programme must not be contingent upon taking part in the research.
5 documentation of the oncology management is standardised and held in such a way that the data are accessible when required which may be 30 years later.

Oncology Units and Assisted Conception Units, storing gonadal tissue should ensure that they develop:

6 full protocols for long term record keeping.
7 consent forms for obtaining tissue.
8 consent forms for the use of tissue for research.
9 consent forms for the use of tissue for research.
10 written material to explain the implications of consent to take tissue, store it and use it in research.

Oncology and Assisted Conception Units should ensure that:

11 when treatment of a child has been successfully completed, there is liaison between the two Units to provide opportunities for explanation and support during adolescence and adulthood prior to the potential use of the preserved tissue (cf Chapter 4).
12 a central registry of all patients completing paediatric oncology treatment is established, so that data can be stored for research and ultimate use in treatment by an Assisted Conception Unit.
13 they use a minimum data set for subsequent use in an Assisted Conception Unit.
14 they use a minimum data set for long-term follow-up so that research can ultimately establish the value of the treatment, biopsy, storage and psychological support regime.
15 these minimum data sets should be developed at a national level.

4

ASSISTED CONCEPTION

Summary

Ovarian tissue cryopreservation is an experimental procedure without documented success. As yet, there is no Health Service funding available for tissue retrieval or storage. Research is required to establish the effective procedures. Organisation of future clinical care of candidates who wish to use their stored tissues will require multidisciplinary input.

CURRENT PRACTICE

Women requesting measures to retain fertility prior to chemotherapy or radiotherapy have the following options:

embryo cryopreservation: stimulated IVF cycle and fertilization of the harvested oocytes with sperm of the husband/partner or donor and storage of the resulting embryos. This technology is well established and has proven success but not many embryos can be obtained from one stimulation cycle. It is only applicable to adult women in a stable relationship.

oocyte cryopreservation: stimulated IVF cycle and storage of the harvested oocytes for later thawing and fertilization. This technology has proven but limited success and not many eggs can be obtained from one stimulation cycle. It is only applicable to post-pubertal women.

ovarian tissue cryopreservation: requires an operative procedure (usually laparoscopic) to harvest ovarian tissue, which contains immature oocytes, but avoids ovarian stimulation. This is an experimental technique with no proven success in humans and limited success in animal models. It is applicable both to prepubertal and post-pubertal females.

ovarian suppression prior to chemotherapy: use of progestogen or GnRH analogues is of unknown value

oophoropexy prior to radiotherapy: appropriate for only a very few patients, requires an operative procedure (laparoscopy) to move ovaries out of the field of pelvic radiotherapy

Ovarian tissue cryopreservation

Women undergoing therapy for malignancy, where there is “intention to cure”, and a high likelihood of therapy-induced premature ovarian failure, are candidates, provided the procedure does not carry excessive risk, if they:

2 have solid tissue malignancy (with no sign of spread e.g. breast carcinoma, osteosarcoma).
Reproductive cancers (breast, ovary) need special consideration as some breast cancer may be oestrogen-dependent with a potential risk from gonadotrophin stimulation, ovarian cancer with storage of the contralateral ovary in ovarian cancer carries a risk of malignancy recurrence if regrafted.
3 have haematological malignancy.
There may be a risk of further disease on regrafting ovarian tissue. It may arise from malignant cells cryopreserved in the tissue initially obtained.

Women may also request ovarian storage if:
38 they have non-malignant conditions and are undergoing chemotherapy, where cytotoxic agents may reduce fertility e.g. severe lupus.

39 have a family history of premature ovarian failure. The woman may request tissue storage at a relatively young age, having no partner, to overcome their possible infertility later in life.
40 if, not being in a relationship, wish to store tissue whilst young to allow future childbearing through assisted conception without age-related loss of fertility and risk of aneuploidy – “social “ requests.

Current regulation of storage and use

Storage of ovarian or testicular tissue, that contains or may contain mature gametes, requires a storage licence under the Human Fertilisation and Embryology Act (1990). Storage without a licence is a criminal offence.

Similarly, therapeutic use of stored gametes, or maturation of immature gametes *in vitro* for the purposes of treatment, requires a licence from the HFEA, and may only be undertaken in premises licensed by the HFEA. Posthumous use of gametes requires appropriate antemortem written consent in accordance with the HFE Act (1990) and the HFEA Code of Practice.

Thus autografting of ovarian tissue does not require an HFEA treatment licence. Experiments to mature oocytes *in vitro* without a view to fertilization or replacement for therapy, i.e. for research, does not require an HFEA licence. However, any attempt to fertilise oocytes *in vitro* for the purposes of research or therapy will fall within the remit of the HFEA.

All storage of mature oocytes requires a licence. Ovarian tissue that does not contain mature oocytes is not subject to the HFE Act – but it does fall within the remit of the Medical Devices Agency Tissue Banking inspection system.

Research proposals must receive approval from an LREC. Consent for use of tissue in research must be obtained. Posthumous use requires antecedent consent from the patient to “gift” the tissue for research.

Preparation of the candidate

Counselling: individuals requesting fertility preservation require counselling and access to adequate facilities. Advice about the relevant aspects of both the oncology and assisted conception must be given.

Screening: exclusion of transmissible disease (HIV, Hepatitis B and C) and the use of quarantine banks for storage will be advised by the HFEA. Screening may not be possible within the time limitations imposed by the imminence of treatment, so separate storage would be necessary until clearance has been effected. That carries an additional requirement for counselling.

Consent: specific consent is required for any procedure that fallsunder the HFE Act.

Collection of ovarian tissue

Collection of ovarian tissue in children requires competence in laparoscopy and should ideally be carried out by a paediatric surgeon. In adult women it is likely to be done laparoscopically by a gynaecologist. Consent for the operative procedure is required and this must be the responsibility of the surgeon. It may be obtained separately from the counselling and consent for tissue storage. Collection of ovarian tissue may be undertaken at the time of operation for the primary malignancy or at insertion of a Hickman line to avoid repeated admission and anaesthesia.

It is as yet uncertain how much ovarian tissue should be removed for storage and what effect removal of that volume of tissue may have on future natural fertility if therapy does not sterilize . It has not been established whether multiple small biopsies (which might contain insufficient follicles), a portion of an ovary or a whole ovary should be removed.

Storage

A system should be implemented for maintaining contact with those patients surviving treatment. It could be similar to that used for HFEA regulated semen storage. A national registry of stored ovarian tissue is recommended

Funding

Funding for these novel procedures is required. This must cover the collection procedure and long-term storage costs. Charging patients already under the stress of cancer treatment is inappropriate.

Covering the costs of fertility preservation under the oncology budget should be explored. The elements of obtaining and cryopreserving the samples should be funded separately from storage, which may need to be long term.

Research

Research into the processes of tissue collection, preparation, cryopreservation and storage are essential if stored ovarian tissue is ever to be used successfully.

Ovarian tissue storage should only be undertaken within a research setting until pregnancy outcome data from cryopreserved samples are available. Ideally some tissue should be taken and stored for research at the same time as tissue is obtained for potential treatment purposes. Information about both research and treatment should be provided during counselling. Separate consents are required.

FUTURE FERTILITY USE

Only a small proportion of tissue samples stored are likely to be utilized for fertility. Among male survivors of cancer, the take-up of stored sperm samples is surprisingly low. There is evidence that survivors of childhood cancers have low rates of marriage. It is possible that one reason for this is their perceived infertility. Cryopreservation would improve survivors' self-esteem and their chances of long-term relationships.

Fitness for pregnancy: some chemotherapeutic agents have cardiac or renal toxicity, and pre-pregnancy review by a "late effects" specialist is recommended. Patients receiving chemotherapy for non-malignant disease may have other issues e.g. renal involvement in systemic lupus erythematosis or heritability of sickle cell disease. These patients should be seen by a Consultant Obstetrician.

Uterine function: it is well recognised that uterine irradiation may affect subsequent pregnancies with risks of miscarriage, premature delivery and fetal growth retardation. Implantation and endometrial response may be impaired. Patients who have received uterine irradiation (e.g. TBI pre-transplant, Wilms' tumour) may require surrogacy.

Follow-up of children born from the new technologies is recommended[4]

Conclusions

1 Embryo cryopreservation is an established procedure.
2 Oocyte cryopreservation has had limited application.
3 Ovarian tissue cryopreservation is an experimental technique; no successful pregnancy has yet been reported in the human, but preservation is intended to create future opportunities for these patients as techniques develop.
4 There are conditions in which ovarian tissue cryopreservation may be valuable.
5 Different regulatory conditions apply to storage and use of cryopreserved ovarian tissue.
6 Technical aspects of ovarian tissue retrieval and storage have not been established.
7 NHS funding for gonadal tissue retrieval or storage has not been defined.
8 Female patients having tissue stored will ultimately require Consultant Obstetrician review before using their stored samples is contemplated.
9 All children born after use of stored tissue should be followed up.

[4] A Central Registry for paediatric data is being considered by the UKCCSG

Recommendations

1 Oncology and Assisted Conception Units should systematically develop research on human ovarian tissue retrieval and storage.
2 Assisted Conception units should have prospective patients evaluated by a Consultant Obstetrician with multidisciplinary input when contemplating use of their stored tissue.
3 Late Effects Clinic should make their patients records available to the relevant Consultant Obstetrician when requested.
4 Representative Bodies should jointly establish a consortium containing a paediatric oncologist, Late Effects specialist, reproductive medicine specialist, clinical scientist, obstetrician and epidemiologist, who should design and carry out follow-up studies of children born after using these procedures.
5 Appropriate Health Service funding should be available for these patients.

5

LABORATORY ASPECTS

Summary

Cryopreservation and storage of mature sperm, oocytes and embryos fall under the aegis of the Human Fertilisation and Embryology Act and the Code of Practice, whereas cryopreservation and storage of immature oocytes and sperm, as well as ovarian and testicular tissue, are regulated by the Dept of Health's Code of Practice for Tissue Banks. Storage facilities, including Paediatric Oncology and Assisted Conception Units, will need to comply with these regulations by April, 2003. Only in this way will the use of immature gametes be assured after that date. Liaison with a certified Tissue Bank by Paediatric Oncology and Assisted Conception Units may facilitate compliance by development of procedures for collection, transport and storage of tissue.

Protection of gametes and germ cells *in situ* from the effects of cancer therapy, while a future possibility, is not currently a successful option, hence current efforts to preserve fertility are focussed on the removal and storage of tissue before therapy commences. Different concerns are raised by the cryopreservation of spermatozoa and oocytes in mature or immature stages, and the regulations pertaining to their storage also differ, so storage for males and females will be dealt with separately.

CRYOPRESERVATION AND STORAGE FOR MALES

Sperm

Mature sperm (interpreted by the Human Fertilisation and Embryology Authority (HFEA) as a haploid male gamete which is able to take part in fertilisation) can be cryopreserved using simple laboratory procedures. Under normal circumstances, the ejaculate is diluted with an appropriate cryoprotectant solution, loaded into labelled vials or straws, and suspended in the vapour above liquid nitrogen for around 15 minutes until the contents are frozen and equilibrated at around -70ºC. The containers are then plunged into liquid nitrogen for long term storage.

Commonly an average of about half of the sperm survive the freezing and thawing procedure, although this is highly variable among individuals. The widespread availability of ICSI now makes it worthwhile to cryopreserve almost all semen samples, even those where sperm have extremely poor characteristics of count, motility and morphology, with reasonable chance of an ultimately successful outcome of later fertility treatment.

The cryopreservation of mature sperm is regulated by the HFEA (see below).

Immature sperm and immature testicular tissue

The cryopreservation of immature sperm, germ cells or immature testicular tissue for boys in whom mature sperm are not produced has not yet been established as a successful clinical treatment. Research is ongoing in this area (Brinster and Avarbock 1994; Schlatt et al, 2000; Brook et al, 2001).

The cryopreservation of immature sperm, germ cells and testicular tissue not containing mature sperm is outside the remit of the HFEA and falls under the Department of Health Code of Practice for Human Tissue Banking (2001)

CRYOPRESERVATION AND STORAGE FOR FEMALES

In adult women, embryo cryopreservation would be the preferred mechanism of retaining fertility potential, provided there is sufficient time before sterilising therapy is to begin, and if a partner is available. If a partner is not available, the insemination of mature oocytes using donor sperm to create embryos for cryopreservation could be considered. This option raises a number of issues, e.g. disposal in the event of the mother's death, the creation of embryos for single women, etc. Careful exploration of the issues and the offer of counselling would be mandatory The procedures of IVF and embryo cryopreservation are widely applied and have a quantifiable success rate when used in adults (HFEA Patients' Guide to Clinics). IVF treatment, embryo formation and cryopreservation must be licensed by the HFEA. They are outwith the The Dept of Health's (DH) Code of Practice for Tissue Banks.

Mature oocytes

For girls beyond menarche, and who are Gillick competent, in whom IVF is inappropriate because of lack of a partner, the possibility of cryopreservation of mature oocytes may be considered. However, this would require a cycle of oocyte collection, usually taking around 4 weeks, and involve the administration of various drugs as well as a surgical procedure for oocyte collection. There is currently no published evidence for using such techniques in minors.

If mature oocytes are available, they can be cryopreserved using techniques similar to those for embryos (Lassalle et al, 1985; Tucker et al, 1998; Fabbri et al, 2000), although the procedure has not yet been fully optimised (Fabbri et al, 2001). Mature oocyte cryopreservation requires the availability of HFEA licensed premises, appropriate series of cryoprotectant solutions and a programmable, controlled rate freezer. Methods of vitrification (extremely rapid cooling), which could avoid the need for a controlled rate freezer by the use of high concentrations of cryoprotectants, are not yet sufficiently reliable and evidence of their safety is incomplete (Kuleshova et al, 1999; Chen et al, 2000). These will require further research before they can be considered for use in treatment.

Mature oocytes cryopreserved using controlled rate methods currently have around a 50% survival chance and a <10% chance of producing a pregnancy (Tucker et al 1998; Porcu et al, 2000). These results were gained in infertile women and the results may differ in patients suffering from cancer.

The storage of mature oocytes is regulated by the HFEA and is outside the remit of the DH Code of Practice for Tissue Banks.

Fully grown immature oocytes

Fully grown, immature oocytes may be collected from regularly menstruating women in whom the ovaries have received minimal or no stimulation with gonadotrophins (Mikkelsen et al, 1999). Such an approach may be considered appropriate in young girls who menstruate, and in whom the effects of ovarian stimulation are uncertain.

Fully grown immature oocytes may be cryopreserved using methods similar to those for mature oocytes (Tucker et al, 1998). This procedure comes under the remit of the DoH Code of Practice, but not the HFEA. However, any subsequent attempts to mature or fertilise the thawed oocytes *in vitro* would be regulated by the HFEA. No treatment licences in this area have yet been granted, however, *in vitro* maturation is applied in several countries using freshly collected immature oocytes, with variable low to moderate success rates (Trounson et al, 1994; Russell et al, 1997; Chian et al, 1999; Mikkelsen et al, 1999; Cha et al, 2000). It is used mostly for women with polycystic ovaries, in whom immature oocyte yields are higher. *In vitro* maturation of fully grown immature oocytes commonly takes around 1-2 days additional time in culture.

The evidence base for pregnancies from embryos cryopreserved as immature oocytes is extremely limited and no advantage over cryopreservation of mature oocytes is apparent. The additional hurdle of

in vitro maturation, which remains suboptimal at present (Trounson et al, 2001), renders this approach experimental, and the potential for detrimental effects upon chromosome movements during oocyte maturation after cryopreservation at an immature stage remains a concern (Park et al, 1997).

Ovarian cortex

The ovarian cortex contains very small primordial follicles comprising the ovarian reserve. The very small oocytes within are immature, non-responsive to gonadotrophins and would take several months to reach maturity. The number of such follicles present is highest in infancy and declines with age. No mature oocytes exist in ovarian cortex, and so this procedure is outside the remit of the HFEA and regulated by the DH according to the Code of Practice for Tissue Banking.

In principle, the cryopreservation of ovarian cortex should allow oocytes to be stored which can then be transplanted back to the patient, after the cancer therapy has been successfully concluded, at a time when fertility is desired. This may be a particularly appropriate option for young girls, in whom the follicle reserve is high and for whom considerable time will elapse before they may wish to use the tissue for fertility, allowing time for improvements and developments of the technique. This potential must be balanced against the uncertainty of the benefit which might accrue, and the risks of the operation. The consultation should include a personalised risk/benefit assessment according to the nature of the condition suffered, its treatment, chances of survival and chances of infertility resulting, as discussed Moreover, a structured detailed discussion between the fertility specialists (clinical and scientific) and the patient and their carers of the rationale behind the technique and its current lack of a successful track record, technical limitations and future prospects should be well documented.

The cryopreservation of ovarian cortex has been applied in animals with demonstrated fertility in a proportion of those into which the thawed tissue has been transplanted (Baird et al, 1999). However, the normal rate of follicle recruitment may be disturbed by the procedure, or the small number of follicles which can be transplanted might render the ovary more akin to one approaching menopause, with a reduced supply of oocytes which are lost at a greater rate (Faddy and Gosden, 1995; Baird et al, 1999). Therefore the longevity of any graft is questionable and will probably depend at least in part upon the size of the tissue available, the number of follicles it contains and the success of revascularisation after transplantation (Nugent et al, 1998).

Research on human biopsies has shown that primordial follicles can survive cryopreservation with good success and that transplantation to immune incompetent animals (Van den Broecke et al, 2001; Gook et al, 2001) or to humans can be carried out (Nugent et al, 1998) with evidence of follicle growth in the grafts. To date, in two attempts to regain fertility using ovarian autotransplants, no pregnancies have resulted although evidence of ovarian function was present (Oktay et al, 2001; Radford et al, 2001).

Ovarian cortex can be removed surgically, in adults via laparoscopy, using a purpose designed biopter (Meirow et al, 1999), which removes shallow circles of cortex of around 5mm diameter. Alternatively, if a part or all of an ovary is resected, this can be processed in the laboratory to yield just the surface cortical layer of around 1-1.5mm thick.

For cryopreservation, the tissue is normally cut into strips up to 5mm wide. These are equilibrated by rolling for 30 minutes at 4ºC in medium with 1.5M dimethylsulphoxide as cryoprotectant, before transfer into vials and cryopreservation using a controlled rate freezer and a program similar to that used for embryos and oocytes (Newton et al, 1996; 1998).

As the tissue is likely to be in storage for many years, it is important to be aware of its quality upon freezing. Moreover, the patient from whom it was removed was to receive therapy for a malignancy, hence it is crucial to check whether the tissue stored might also contain malignant cells. In such an event, transplanting it back would be inadvisable as it would risk reintroducing the cancer (Shaw and Trounson, 1997). To this end, a small sample of the fresh tissue and a small test thaw sample should be processed to check for follicle density, follicle survival after thawing and to search for evidence of malignant cells. The latter should be assessed by a qualified histopathologist. While variation among the different areas of the cortex is expected (Cortvrindt and Smitz, 2001), the results will provide some indication of the quality of tissue and its likely post-thaw viability, and hopefully provide reassurance with respect to the possibility of contamination with cancerous cells. This information will enable the patient to make an informed decision in due course about the use of the tissue.

If tissue is recovered and stored but its use in autotransplantation is inadvisable for some reason, future developments in *in vitro* culture of primordial follicles may accrue to the point where, in several years' time, *in vitro* production of mature oocytes may become a possibility (Liu et al, 2000; Hovatta, 2000). Moreover, methods of *in vitro* destruction of contaminating malignant cells might be developed which might render previously unsafe tissue suitable for autotransplantation. While such developments are still a long way off, young patients may have many years before fertility is desired, so their tissues should be kept in storage even though the prospects of using some of them are currently remote.

REGULATION

HFEA regulated storage

Patients having 'mature gametes' or embryos cryopreserved under HFEA regulations require to be assessed according to a variety of measures, including, for example, the provision of informed consent, and will (from December 2004) require to be screened for transmissible diseases, currently including Hepatitis B and C, and HIV (HFEA, 2001). The decision, whether to store tissue from or treat patients screening positive for such conditions, will remain with the clinic. If/when the gametes are required for any HFEA licensed treatment procedure (IVF, ICSI) the patient will be reassessed for 'welfare of the child' considerations (HFE Act 1990) and any treatment provided will be under HFEA licence and according to the prevailing legislation. Hence, the provision of treatment is not guaranteed, even if gametes are stored.

The centres in which the gametes are stored will be licensed and inspected by the HFEA in accordance with its own guidelines arising from the HFE Act (1990). These are principally concerned with the safety, security and protection from cross-contamination of samples, including, for example, requirements for the person in charge of the cryopreservation facilities to be adequately trained and experienced, the availability of customised secure dedicated facilities, appropriate emergency procedures for storage vessel failure and the availability of standard operating procedures. There are a number of practical concerns among professional groups about various aspects of the guidelines, including problems with quantifying the extremely small risk of cross contamination for different tissue types required for patient information, the lack of availability of vessel cleaning procedures known to be non-toxic to stored gametes or embryos, and the lack of methods suitable for assessing microbiological hazards within tanks and liquid nitrogen sources.

Persons having mature gametes stored are registered with the HFEA. The time for which gametes may be stored is determined by the HFE Act, 1990 and should be checked. Patients undergoing gamete storage must take decisions prior to storage about what should happen to any material remaining in storage at the time of death or incapacity.

Medicines Control Agency (MCA) Regulated Storage

The Department of Health regulates storage of immature gametes and other tissues of human origin for therapeutic purposes, (but notably excluding human embryos and mature gametes, via its Code of Practice for Human Tissue Banking, 2001). The Code covers tissue banks within the UK public sector supplying human tissues for therapeutic purposes to the health service. Such tissue banks will require to be accredited by the Department of Health inspectors by April 2003. The accreditation system is based on a total quality management approach requiring a high level of documentation, air quality control, infrastructure, microbiological monitoring and aspects of process control which relate to good practice in manufacturing.

The code does not relate directly to private centres at present, although these can also apply for accreditation, however, patients will need to be made aware of their opportunities and any restrictions on using their tissue after April 2004 if it is stored in non-accredited banks. Questions have been raised by the Association of Clinical Embryologists with the DH in respect of whether tissue from non accredited banks may be used in NHS transplant operations, however, this is likely to be a matter for individual Trust boards, and no firm conclusion was reached. Again, there are a number of concerns about the Code of

Practice as it may relate to the storage of immature gametes in assisted conception centres for autotransplantation or other therapeutic purposes, however, these are unlikely to be resolved until the Code has been in operation for some time and the accreditation process becomes clearer. Collaboration between established, accredited Tissue Banks and Assisted Conception Units may promote optimum methods of storage and facilitate accreditation. However, as at 1 March, 2002, no tissue bank had achieved accreditation. At a seminar held at the University of Warwick on that day, extensive discussions between delegates from Assisted Conception Units and representatives of the MCA, the Working Group on the Code of Practice for Tissue Banks and the Head of a Tissue Bank, which had applied for accreditation, concluded that Assisted Conception Units would be unlikely to achieve accreditation in their own right. Major investment would be required to achieve this objective, which was unlikely to be feasible in the absence of funding for storage of immature gametes and the low throughput of patients currently being offered cryopreservation.

Funding

At present, NHS funding for sperm storage for male cancer patients is sometimes available, but funding for ovarian cortex storage or other options for female patients is rare. These procedures are currently performed in a variety of public and private settings with the intention of providing patients with a compassionate service, often in the absence of funding. The introduction of new regulations relating to the necessary standards of any service provided will impact upon the investment required and may result in a much reduced service for deserving patients.

It is the view of this Working Group that more formal attention should be paid to cancer patients' needs for appropriate and customised fertility services, in line with a modern approach to cancer treatment and with a view to the government's stated objective of equalising provision of healthcare across the country.

Conclusions

1 The methodology of cryopreserving mature or immature female gametes or mature male gametes in a lab is straightforward, however the regulatory framework surrounding these developments is extensive and complex.
2 The Dept of Health published a Code of Practice for Tissue Banks Providing Tissues of Human Origin for Therapeutic Purposes (CoP) in March, 2001.
3 The CoP, based on a series quality systems approach, applies to tissue banks in the public sector.
4 The CoP applies to immature gametes, but excludes embryos and mature gametes, so it is directly relevant to Paediatric Oncology and Assisted Conception Units.
5 There are major cost and organisational implications for Paediatric Oncology and/or Assisted Conception Units.

Recommendations

Oncology and Assisted Conception Units should:
1 familiarise themselves with the Tissue Banks Code of Practice.
2 develop plans and procedures, documentation and training programmes to comply with the HFEA Code of Practice.
3 consider developing these procedures in conjunction with a certified Tissue Bank.

The Government should:
4 Provide a comprehensive nationwide service covering the initial freezing and long term storage of mature sperm for men and competent boys facing sterilising therapy.
5 Develop appropriate fertility-preserving services for others facing sterilising therapies, including girls, women and prepubertal boys.
6 Enable tissue banks storing reproductive tissues to achieve accreditation according to the Dept of Health Code of Practice for Tissue Banks.

6

PSYCHOSOCIAL ASPECTS

Summary

Psychosocial aspects of childhood cancer management are important and need to be dealt with by an appropriate child mental health specialist with relevant experience in paediatrics, oncology and reproductive medicine. Such a specialist should contribute to the paediatric oncology team discussion. Psychosocial support needs to be accessible to survivors long after the completion of their successful treatment. Liaison between Paediatric Oncology and Assisted Conception Units should be encouraged so that each unit's requirements are recognised by the other.

A range of psychosocial interventions takes place in a number of environments within Paediatric Oncology services, in Late Effects Clinic with the parents and in Assisted Conception Clinics with the child and the parents. There is a need for information and explanation with emotional support over a long period and this will extend to the Assisted Conception unit with or without an intended partner.

Psychosocial and counselling issues
Offering psychosocial support and the necessary information on which to base decisions, and managing this in the appropriate individual and relational contexts at the time of diagnosis is a difficult enough task with adults facing a life threatening or fertility damaging diagnosis. Where the patient is a child this raises a number of additional particularly complex issues, e.g. children's involvement in the consent process and their capacity to consent, the uncertainties regarding the potential success of any measures taken to increase the chances of having a child with their own gametes many years into the future, the experimental nature of the intervention and the need for research into this area to confirm the viability of gamete storage long term.

Adults
In adult oncology, those engaged in a psychosocial support role should have knowledge and expertise in cancer and its emotional and psychological effects, and sufficient understanding of assisted reproductive technology to contribute to the process of decision making with patients and their partners to make informed decisions. Although ongoing support may be indicated throughout the period of diagnosis and treatment, the contribution of a psychosocial specialist will be particularly important in relation to fertility issues both at an early stage, and in due course when the individual or couple wish to explore the options available to them for family creation. It is also crucial that appropriate therapeutic work is offered to allow the individual to deal with the emotional consequences post-treatment and to begin the process of adjusting to whatever new realities exist in relation to his/her compromised fertility.

Children and young people
It has been shown that children can be helped to understand and participate in treatment decisions (Alderson, 1993). Joining in the decision making process may improve later adjustment (Cooklin, 1989). Lansdown (1998) stresses the importance of clarifying each child's level of understanding about illness and treatment, finding out what they want to know and how much they wish to participate in relevant clinical decisions. The latter will necessarily depend on individual factors, such as previous experiences of illness and the usual process of decision making within the family.

Working with children demands considerable understanding of cognitive, emotional and psychological development, expertise in talking to children and young people (alone and with their families) at times of stress and family crisis, and skill in enabling families to explore difficult issues. In particular, young people may need help to enable them to pose questions or express views that might oppose those of their parents. Informed consent includes ensuring that the implications of both doing and not doing are understood. Alongside the vital priority of medical care, there needs to be sufficient consideration of the psychological and emotional wellbeing short and long term, and the need for careful, sensitive family work around the process of decision making.

Child mental health professionals have been considering the issue of 'sufficient understanding' in relation to the assessment of 'Gillick' competence (see Reder and Fitzpatrick, 1998). The outcome of this assessment carries particular implications in relation to the storage of gametes, an instance of a reproductive right (Deech, 1998) for which proxy consent will not suffice. Alongside this, is the prevailing view (supported by the Convention on Children's Rights - Article 12b, the Children Act, 1989 and the Human Rights Act, 1998) that children need to be enabled to participate in treatment decisions. They need to be helped to express a view which should be incorporated into the decision making process, even when they do not pass the Gillick test. The weight that this is given may depend on the importance of the decision, his/her age, and whether the issue is one affecting quality or quantity of life (Devereux et al., 1993).

Consent has to be a dynamic and interactive process, based on giving the child information in a way that s/he can understand and think about, and participate in a way that s/he feels negotiated with. This is a particular challenge at a time when this task competes with plans to start treatment with fertility damaging, but life-saving agents. Ideally multiple opportunities should be available within a short period of time. There may be cultural and/or religious issues to be considered, and the family's usual way of involving (or excluding) offspring from decision making may be challenged. Consideration should be given to the involvement of interpreters, if fluency in English is insufficient to deal with these issues – children should not be expected to act as interpreters for their parents.

In conversing with children and young people about complex issues, it is helpful not to assume their level of understanding or experience. A dialectic (rather than didactic) approach allows the child to explain or describe what s/he knows, explore questions and express a different opinion. It needs to be made explicit that compliance with adults' views is not being sought. New information needs to be given in a way that s/he can understand and is 'imaginable', and questions asked that are easy to answer. Sufficient space should be set aside for questions and attention paid to anxieties or conflicts around the decision. Where treatments are unproven or experimental this should be made clear. Objections raised by the child/young person should be taken seriously and included in further discussion. In addition to these points, Cooklin (personal communication, 1999) suggested that helping the child/young person to construct a list of 'Pros' and 'Cons' allowed thinking about both perspectives.

Further opportunities should be made available to young people and their families to discuss these issues after decisions have been taken.

Once again, psychosocial support may be critical in helping the young person and his/her family through the treatment regime and any surgery. In relation to reproductive health, there are at least two points at which this may need to be more fully addressed for long-term survivors. The first is during adolescence, when sexuality, relationships with peers and the opposite sex are prominent issues. It is clear from existing research that young people experience difficulties in these areas. This may be another time when it is important to address the young person's understanding of 'fertility' – and the difference between this and 'potency'. The second is in adulthood when facing the options about family creation may emerge as reality, at this time it is most likely that the individual or couple will access this help through an Assisted Conception unit.

Suggestions

Services should seek out a suitably skilled and knowledgeable individual from a mental health profession (child clinical psychologist, child and adolescent psychiatrist with an interest in paediatric liaison, an experienced family therapist or social worker with specialist therapeutic training) to be part of the treatment team. This person will need to draw on knowledge of children's cognitive and emotional development and have expertise in working with families in distress. In addition, they will need to have (or develop) an awareness of fertility issues. Religious or cultural beliefs must be considered and handled

sensitively (for example, masturbation may be forbidden in some contexts but accepted in these extreme circumstances). This person can, with other members of the team engage the child/young person and his/her family in the exploration of the issues and support them in the process of decision making. The involvement (and additional training) of members of the nursing team may be of significant benefit, because of their accessibility and their role in the young person's ongoing care.

If this work is undertaken by a person whose experience is in the context of an Assisted Conception unit, s/he must be adequately trained in working with families and have the skills in communicating with children. This would need to include an assessment of the child's existing knowledge and understanding about the body, illness and Conception, and being able to find age-appropriate ways to explain concepts, treatments and possibilities.
The development of written or audio-visual information may help young people and their parents absorb complex information and help the process of discussion and decision making. For example the UCLH leaflet on Sperm Banking (2000), (see Appendix III) is written in easy, teenager-friendly language. Clarity and transparency are important –people should be informed of treatments currently available, possible future developments and the experimental nature of taking immature gametes or freezing tissue long term.

Separate consent forms should be developed for young people where their consent is sought, and for parents, where very young children are being treated.

Alongside the need for medical and biological research in this area, psycho-social issues need to be recognised and explored. Relevant research (for example, on children's understanding of infertility, currently in progress (Balen et al.), and a pilot project interviewing male adolescents about their experience of sperm banking (Crawshaw et al.) will be vital in helping to develop sensitive and appropriate interventions in this area.

Conclusions

1 Understanding by the child of the complex issues involved leads to a determination of whether a child has the legal competence to make a decision (Gillick competence).
2 The Gillick status of a child determines whether or not the child can give consent to obtaining tissue and to its (cryo)preservation.
3 A psychosocial specialist should be involved in support and therapeutic work to help the child deal with the uncertainties.
4 Discussions are needed before and after decisions are made.
5 Further discussion of the fertility and other reproductive issues will be required in adolescence and adulthood.
6 Paediatric and clinical reproductive experience are required by psychosocial specialists in dealing with these patients.
7 Special consent forms and written information are required for these children and young people.

Recommendations

Oncology Units should ensure that:
1 they have a psychosocial specialist in their team to deal with these psychosocial aspects of cancer care.
2 psychosocial specialists working in oncology units obtain appropriate paediatric and reproductive medicine experience.

Oncology and Assisted Conception Units should ensure that:
3 arrangements are made for childhood cancer survivors to have access to further psychosocial support during adolescence and adulthood from Oncology and/or Assisted Conception Units.

7

ETHICAL ASPECTS

Summary

The relative risks and benefits of gonadal tissue retrieval and preservation have not been established. Written explanations and consent forms for (Gillick) competent individuals and proxy consent forms for (Gillick) non-competent individuals need to be developed. Uncertainty about technical procedures should be resolved by research protocols. These should be submitted to the appropriate research ethics committee.

The ethical issues relating to future reproduction for survivors of childhood cancer have been well described in a series of publications: Nugent et al. (2000); Spoudeas and Wallace (2001); Grundy et al. (2001). They fall into three categories:

Risks and experimental nature of procedures

1 Risks: these may be surgical, associated with the intervention required to obtain the gonadal samples; from progression of the disease engendered by delay in initiating treatment necessitated by the additional time needed for further counselling and the biopsy procedure; damage induced by the gonadotoxic therapy if samples are obtained after the therapy has begun and the possibility of passing on any genetic damage induced by that therapy; they may be psychological, by raising hopes and failing to fulfill them.
2 Experimental: most of the above risks have not been quantified; there is considerable uncertainty about subsequent fertility or the harm that intervention may cause.

These risks differ for males and females and discussion should specify separately the risks of each.

Consent issues

1 Patients given a diagnosis of cancer are stressed and vulnerable. This raises the question of the validity of any consent given.
2 For a Gillick non-competent individual proxy consent needs to show a net benefit for the child.
3 Retrieval and cryopreservation of gonadal tissue require consent separate from that for subsequent use of that tissue.
4 Consent should be discussed and obtained prospectively for appropriate disposal of tissue in the event of death.

Policy issues

1 There should be regulatory control of procedures and use of gametes. (The Dept of Health has announced its intention to legislate to give the HFEA the power to permit storage of gametes where consent has been given, so long as the gametes can be removed lawfully (subject to parliamentary time being available).
2 All clinics should act in accordance with a Code of Practice. This should include counselling.
3 There are many uncertainties about procedures and outcomes. These should be resolved by formally established research protocols.
4 These research protocols should be developed in centres by multidisciplinary collaboration and should all have been subjected to appropriate research ethics committee surveillance.

Conclusions

1 Most risks associated with obtaining tissue for cancer patients have not been quantified, so these procedures should be described as experimental.
2 For a Gillick competent individual separate consents are required for retrieval and cryopreservation and for subsequent use of that tissue.
3 For a Gillick non-competent individual proxy consent needs to show a net benefit for the child.
4 Prospective consent is required for appropriate disposal of tissue in the event of death or incapacitation.
5 Research protocols should resolve uncertainties about procedures.
6 Specific research protocols should be restricted to a few centres and subjected to appropriate ethics committee surveillance.

Recommendations

Oncology and Assisted Conception Units should ensure that:

1 consent forms describe the experimental nature of all gonadal tissue retrieval and preservation.
2 consent forms explain the need for additional future consent for use of stored material.
3 consent is required, in the event of death, for use of tissues in research.
4 consent is required, in the event of death, for disposal of tissues.
5 they consider developing consent forms for proxy consent.
6 a consortium of paediatric oncologists, paediatric surgeons, reproductive medicine specialists and appropriate clinical and laboratory scientists establish research protocols for tissue retrieval and cryopreservation techniques.
7 the consortium should approach the appropriate ethics committees (according to the NHS guidelines, if the research is to be carried out in the NHS) and submits the research protocols to them.

8

LEGAL ASPECTS

Summary

25 *Storage and use of live human mature gametes is regulated by the Human Fertilisation and Embryology (HFE Act 1990) and the HFE Authority. The HFE Act 1990 requires written consent from the person providing the mature gametes after s/he has been given proper information and appropriate opportunities for effective consent. The statute does not permit proxy consent for adults or children who are unable to give effective written consent. The HFE Act 1990 only governs the storage and use of material which consists of or contains mature human gametes or embryos. The retrieval of mature gametes and human tissue and the storage and use of human tissue that does not contain mature gametes is governed by the common law and, in the case of children, by child law statutes.*

35 *The McLean Review (1998) has proposed that the HFE Act 1990 be amended to allow the HFE Authority power to waive the requirement for consent for storage of mature gametes where the person is incompetent and the gametes have lawfully been removedin his/her "best interests It might be considered appropriate to seek a court's authorisation to proceed in all such cases, regardless of the age of the incompetent person. The waiver of statutory requirements for consent from the gamete provider would not include the use of mature gametes. Once the person (re)gained the ability to give a legally valid consent, continued storage and research upon or use of the gametes would be dependent on obtaining an effective consent from him or her.*

45 *Since the removal, storage and use of material which does not contain mature gametes is not governed by the HFE Act 1990 or HFE Authority, it may be possible for parents to consent on the child's behalf to retrieval and storage of such tissue, provided this is deemed to be in the child's best interests. Parents may also be able to consent to research upon removed reproductive tissue, although this is likely to depend on the research being deemed to be in the child's best interests or at the least, not against the child's interests. It is unlikely that retrieval or storage can or should proceed in the face of objection by the child, even if the child were incompetent to give a legally valid consent to or refusal of medical treatment.*

55 *Seeking to preserve the child's reproductive potential is likely to be considered a substantial benefit to the child, given the recognition of the importance of reproductive rights. However, whether it is in the child's best interests to remove and store his/her tissue will depend upon a consideration of many factors such as the risks of the retrieval procedure, both physical and psychological; the effect this may have upon the treatment of the child's cancer; the likelihood of the loss of fertility as a result of cancer treatment; the availability of alternative methods of conserving fertility and the prognosis for the child.*

For a more extended description see **Appendix II**

Recommendations

The **Government** should:

1 Implement the recommendations of the McLean Review to enable the effective consent provisions in the HFE Act 1990 to be waived in respect of children and adults who are unable because of

incapacity to give effective consent to storage of their mature gametes or tissue containing mature gametes.

2 If legislation is amended to give the HFEA the power to waive the effective consent provisions of the HFE Act 1990, whether removal of mature gametes or reproductive tissue for future fertility treatment from an incompetent person of or over the age of 16 in Scotland, or of or over the age of 18 in England and Wales, **requires to be considered by a court**, clarify such matters in advance, through legislation.

3 In addition, if legislation is amended to give the HFEA the power to waive the effective consent provisions of the HFE Act 1990, whether removal of mature gametes or reproductive tissue for future fertility treatment from an incompetent person under the age of 16 in Scotland, or under the age of 18 in England and Wales, requires to be considered by a court **or whether this may be authorised by the person's parents**, such matters should be clarified in advance, through legislation Consider whether any research upon reproductive tissue containing immature gametes,, reproductive tissue containing mature gametes or mature gametes should be allowed to take place during the period of the gamete provider's incompetence and, if so, whether this could be authorised by parents (in the case of children) or a court.

4 Confirm whether competent children under the age of 18 in England and Wales or 16 in Scotland can give a legally valid consent to removal, storage and use of reproductive tissue that does not contain mature gametes and whether this decision must be in the child's best interests.

9

NHS FRAMEWORK

Summary

Within the NHS Framework for Cancer Services, the services for retrieval and storage of gonadal tissue or gametes from cancer sufferers about to undergo treatment for their cancer have not yet been considered. Funding has not been specifically allocated.

The NHS Cancer Plan (Calman -Hine Report) was presented in 1995.

Cancer networks

Cancer networks are the organisational model for cancer services to implement the Cancer Plan. Thirty four cancer centres/networks, each covering a population of *ca* 1.2 million have been established. The networks will work together to develop all aspects of cancer services, each network having a Lead Manager, Clinician and Nurse. A set of Service Improvement Guides (Ref. 2 web address), which summarise the lessons learned by pilot projects, have been published and set out principles for making changes. Health Authorities, PCTs and service providers will together look at the investment in cancer services required to implement the network strategy. Regional Specialist Commissioning Groups are responsible for commissioning aspects of care. Not all aspects will be provided in every cancer network. Preservation of fertility must be included. This will improve the quality of the overall treatment package for these sufferers.

Working Group Meetings have been held as part of the national Defining Specialised Services Project, on Women's Health, Infertility, Paediatric Oncology and Haematology, where the issues involved in fertility preservation for those about to undergo cancer treatment have been highlighted.

Cancer Information Advisory Group (CIAG)

From the NHS Cancer Plan a number of developments have taken place. A Cancer Information Advisory Group has been established. This is a Group chaired by the National Cancer Director and made up of a range of experts in the field of information development and delivery. It also includes patient representatives. The Group's main aims are to draw together a directory of existing written information, and to identify any gaps, to draw up guidance on what makes good information and to provide input on the issues of how and when patients should receive information. This material should contain information relevant to preservation of fertility.

Cancer Services Collaborative (CSC)

The CSC is co-ordinated by the National Patients' Action Team (now part of the Modernisation Agency). It aims to improve the experience and outcome of care for patients with suspected or diagnosed cancer by optimising systems of care delivery. The CSC brings together clinical and management teams from cancer networks across the NHS. Teams are redesigning the care process for patients with or suspected to have one of five common cancers: breast, lung, bowel, ovarian and prostate. The CSC aims to support

the reduction in waiting times and achieve booking targets in the NHS cancer Plan. It will also support the implementation of Calman-Hine and highlight lessons from which the wider NHS can benefit.

The Cancer Services Collaborative needs to emphasise the importance of describing and providing access to preservation of fertility. This will enablethese sufferers to envisage fulfilling their potential for reproduction

National Institute of Clinical Excellence (NICE)

The formal remit of NICE is to promote clinical excellence and the effective use of available resources in the NHS. NICE will do this by issuing authoritative evidence-based guidance on clinical practice. Broadly, there will be three forms of guidance: clinical guidelines (management of particular clinical conditions), appraisal guidance (guidance on specific health interventions, including pharmaceuticals) and audit methodologies.

NICE has recently published the Scope of a "Guideline on the Assessment and Treatment for People with Fertility Problems". With respect to the population to be covered, it states that " the guideline will offer advice on the management of people with a known condition for their fertility problems, for example, prior treatment for cancer…". However this will only operate when a couple present with infertility, clearly some years after the decision on reproductive tissue cryopreservation needs to have been made. At present there are too few data in this area to be able to give evidence-based guidance. By the time limited data have been accumulated a generation of cancer sufferers may have lost the ability to reproduce.

Children's cancer

The NHS Plan set out the intention to make authoritative guidance on all aspects of NHS cancer care. Building on the Improving Outcomes series of cancer guidance reports (see Ref. 2 web address), NICE will commission a comprehensive package of guidance on cancer services covering all cancers, including those affecting children and adolescents, over the next three years, which all health authorities and NHS trusts will be expected to implement. The potential for tissue cryopreservation and the research required to improve it, should be taken into account.

Conclusions

1 Services involved in the retrieval and storage of gonadal tissue or gametes from cancer sufferers about to undergo treatment for their cancer so far have not been defined.

2 There has been no definition of responsibilities or of funding for these services.

Recommendations

For those about to undergo cancer treatment:

1 the Cancer Information Advisory Group should be aware of and publicise literature available on preservation of fertility.

2 the Cancer Services Collaborative should emphasise the importance of describing and providing access to preservation of fertility.

3 the Cancer Networks should be able to identify at least one centre in each network from which advice can be obtained and the necessary procedures undertaken for preservation of fertility.

10

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12

Summary of Recommendations

Oncology Units should ensure that:

1 all competent males, who can produce semen, have the opportunity of discussing the preservation of their fertility with an appropriately trained person.
2 all competent females have the opportunity of discussing the preservation of their fertility by conservation of a sample of gonadal tissue or oocytes with an appropriately trained person prior to gonadotoxic therapy or removal of ovarian tissue.
3 the parents of Gillick non-competent children are given the opportunity of discussing the issues relating to their children's gonadal tissue conservation and agreeing an appropriate course of action.
4 in addition to obtaining consent for gonadal tissue conservation, where appropriate, the rationale and need for relevant research should be explained. An attempt should be made to seek consent to use a part of the tissue for research, but participation in the programme must not be contingent upon taking part in the research.
5 they have a psychosocial specialist in their team to deal with the psychosocial aspects of cancer care.
6 psychosocial specialists working in oncology units obtain appropriate paediatric and reproductive medicine experience.
7 documentation of the oncology management is standardised and held in such a way that the data are accessible when required e.g. 30 years later.
8 they use full protocols for long term record keeping.
9 they use a minimum data set for subsequent use in an Assisted Conception Unit (see Rec. 33).
10 they use a minimum data set for long-term follow-up so that research can ultimately establish the value of the treatment, biopsy, storage and the psychosocial support regimes (see Rec. 34).

Oncology Units (<u>and</u> Assisted Conception Units, if so involved) should ensure that:

11 a central registry of all patients completing oncology treatment is established, so that data can be stored for research and ultimate use in treatment by an Assisted Conception Unit.
12 when treatment of a child has been successfully completed, there is liaison between the two Units to provide opportunities for explanation and psychosocial support during adolescence and adulthood prior to the potential use of the preserved tissue.
13 they develop consent forms for obtaining tissue.
14 they develop consent forms for storage of tissue
15 they develop consent forms for the use of tissue in research where appropriate.
16 they use written material to explain the implications of consent to take tissue, store it and to use it in research.
17 the consent forms describe the experimental nature of all gonadal tissue retrieval and preservation.
18 the consent forms explain the need for additional future consent for use of stored material.
19 consent is required, in the event of death, for disposal of stored tissues.
20 consent is required, in the event of death, for use of tissues in research.
21 they consider developing consent forms for proxy consent.
22 all written information is appropriately reviewed and piloted.
23 they consider their need to register under The Data Protection Act (1998)

Oncology and Assisted Conception Units should:

24 familiarise themselves with the Tissue Banks Code of Practice.
25 develop plans and procedures, documentation and training programmes to comply with the Code of Practice.
26 consider developing these procedures in conjunction with a certified Tissue Bank.
27 systematically develop research on human ovarian tissue retrieval and storage.
28 Assisted Conception Units should have prospective patients evaluated by a Consultant Obstetrician with multidisciplinary input when contemplating use of their stored tissue.

29 Late Effects Clinics should make their patients' records available to the relevant Consultant Obstetrician when requested.

Representative Bodies should jointly establish:

30 a consortium containing a paediatric oncologist, late effects specialist, reproductive medicine specialist and clinical scientist, an obstetrician and an epidemiologist to design and carry out follow-up studies of children born after using these procedures.
31 a consortium of paediatric oncologists, paediatric surgeons, reproductive medicine specialists and appropriate laboratory scientists to establish research protocols for tissue retrieval and cryopreservation techniques.
32 the consortia should approach the appropriate research ethics committees (according to NHS Guidelines if the research is to be carried out in the NHS) and submits the research protocols to them.
33 a minimum data set for subsequent use in an Assisted Conception Unit .
34 a minimum data set for long-term follow-up so that research can ultimately establish the value of the treatment, biopsy, storage and psychosocial support regimes .

For those about to undergo cancer treatment:

35 the Cancer Information Advisory Group should be aware of and publicise literature available on preservation of fertility.
36 to improve the overall treatment package for these sufferers the **Cancer Services Collaborative** should emphasise the importance of describing and providing access to preservation of fertility.
37 the **Cancer Networks** should be able to identify at least one centre in each network from which advice can be obtained and the necessary procedures undertaken for preservation of fertility.

The Government should:

38 implement the recommendations of the McLean Review to enable the effective consent provisions in the HFE Act 1990 to be waived in respect of children and adults who are unable because of incapacity to give effective consent to storage of their mature gametes or tissue containing mature gametes.
39 if legislation is amended to give the HFEA the power to waive the effective consent provisions of the HFE Act 1990, for removal of mature gametes or reproductive tissue for future fertility treatment from an incompetent person of or over the age of 16 in Scotland, or of or over the age of 18 in England and Wales, **needs to be considered by a court**, clarify such matters in advance, through legislation.
40 consider whether any research upon reproductive tissue containing immature gametes, reproductive tissue containing mature gametes or mature gametes should be allowed to take place during the period of the gamete provider's incompetence and, if so, whether this could be authorised by parents (in the case of children) or a court.
41 confirm whether competent children under the age of 18 in England and Wales or 16 in Scotland can give a legally valid consent to removal, storage and use of reproductive tissue that does not contain mature gametes and whether this decision must be in the child's best interests.
42 provide a comprehensive nationwide service covering the initial freezing and long term storage of mature sperm for men and competent boys facing sterilising therapy.
43 develop appropriate fertility-preserving services for others facing sterilising therapies, including girls, women and prepubertal boys.
44 by providing funding, encourage tissue banks storing reproductive tissues to achieve accreditation according to the Dept of Health Code of Practice for Tissue Banks.

provide Health Service funding for fertility preservation in children with cancer.