

FERTILITY PRESERVATION
FOR CANCER PATIENTS
WITHIN
THE SUSSEX CANCER
NETWORK

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1 NICE GUIDELINES:

1. Before commencing chemotherapy or radiotherapy likely to affect fertility, or management of post treatment fertility, the procedures recommended by the Royal College of Physicians and the Royal College of Radiologists should be followed.
2. Men and adolescent boys preparing for medical treatment, which is likely to make them infertile, should be offered semen cryostorage because the effectiveness of this procedure has been established.
3. Local protocols should exist to ensure that health professionals are aware of the value of semen cryostorage in these circumstances, so that they deal with the situation sensitively and effectively.
4. Women preparing for medical treatment that is likely to make them infertile should be offered oocyte or embryo cryostorage as appropriate if they are well enough to undergo ovarian stimulation and egg collection, provided this will not worsen their condition and that sufficient time is available.
5. Women preparing for medical treatment that is likely to make them infertile should be informed of oocyte storage has very limited success and that cryopreservation of ovarian tissue is still at an early stage of development.
6. People preparing for medical treatment which is likely to make them infertile should be offered counselling from someone who is independent of the treatment unit to help them cope with the stress and the potential physical and psychological implications for themselves, their partners and any potential children resulting from cryostorage of gametes and/or embryos.
7. Where cryostorage of gametes and/or embryos is to be undertaken because of medical treatment that is likely to make people infertile, this should occur before such treatment begins.

2 INTRODUCTION

Infertility services in the United Kingdom are based upon the premise that infertile couples are not ill. In the past, infertility issues have been seen as life style problems rather than health problems and in many ways this has been reflected in funding through the national infertility service. Even now there is extensive private provision within this sector, with half of all clinics being privately run. There is also considerable evidence of a post code lottery within provision of fertility services and there can be no doubt that this is partly because private clinics are an integral part of this service and therefore tend to be located where profits are likely.

With the publication of NICE Guidance on the applications of cryopreservation in cancer treatment, the emphasis on life style versus health issues within

fertility must shift. Clearly Oncologists must be aware of situations where their treatment will affect fertility in patients who are being treated for cancer and they must also be aware of the process of access into services and facilities available for cryopreservation of gametes and/or embryos. The NICE Guidance has developed on the back of a working party from the Royal College of Physicians and the Royal College of Radiologists, which has recommended the procedures that are to be followed before commencing chemotherapy and radiotherapy which are likely to affect fertility; and also the management of post treatment infertility. The British Fertility Society has recently produced a strategy for developing policy and practice in fertility preservation for survivors of cancer.

It must be remembered that the NHS will currently only fund one cycle of IVF for any woman with infertility and this is only available to women who satisfy strict inclusion criteria including no previous children to either partner and age less than 40 years.

3 CANCER PATIENT MANAGEMENT AND ITS IMPACT ON FERTILITY:

The following section of this paper is designed to inform the reader of the numerous ways in which therapies designed to treat cancer can impact on the patient's fertility. Although precise evidence is lacking in many areas, wherever possible, references have been cited to support figures shown and conclusions made.

1).SURGICAL MANAGEMENT

Surgery can impact on fertility in one of two ways. It can either render someone infertile by removal of reproductive organs or in the case of the male it can interfere with potency or ejaculation. There is no doubt, however, that in recent years there has been tendency towards more conservative treatment for many malignancies affecting the reproductive organs.

i) Female Patients

In women, there has been tendency towards less radical approaches to cancer of the cervix with the development of loop excision techniques for very early cervix cancer and more recently the development of the radical trachelectomy which allows a radical approach to cervix cancer that is treatable surgically, but with preservation of uterus and thus fertility. Endometrial cancer is commonly a disease of the post-menopausal group or at least in those who have had completed their family, and therefore it is unusual for treatment of this disease, which does involve hysterectomy and bilateral oophorectomy, to impact upon fertility. Epithelial ovarian cancer continues to be treated radically with loss of reproductive organs but increasing understanding of germ cell malignancies and borderline tumours of the ovary has led to the more conservative approach to these neoplasms and often a single oophorectomy will be performed where in the past, a hysterectomy and / or bilateral oophorectomy would have been the treatment of choice. It is unusual for vulval carcinomas to be seen in the reproductive

age group, and although they may have major psychosexual impact it would be unusual for a surgical approach to these to impact upon fertility.

ii) Male Patients

Testicular cancer is the major cancer affecting the reproductive organs of the male and the majority of these are treated with a unilateral orchidectomy and staging thus preserving reproductive capacity. Other tumours affecting the reproductive organs in the male tend to occur in a much older age group where fertility issues may not be of importance. Surgery for other pelvic malignancy such as bladder, prostate and rectum can clearly interfere with potency or ejaculation; however, the age dependency of these tumours would suggest that most occur in an older group of patients where fertility issues are unlikely to be of major importance. Thus fertility services are unlikely to be as important to this older group of individuals.

2). CHEMOTHERAPY EFFECTS ON FERTILITY

Chemotherapy can produce significant effects upon patient fertility. These affects are dependent on a number of factors: -

- i) **Radical versus adjuvant chemotherapy.** Radical chemotherapy generally having more profound effects on fertility than adjuvant chemotherapy.
- ii) **Single agent versus combination chemotherapy.** Increasing complexities of regimes are more likely to have impacts upon fertility than single agent
- iii) **Dose dependent affects.** Increasing doses in principal are likely to have more profound affects on fertility than lower doses.
- iv) **Drug dependent effects.** Different agents have a markedly different impact upon fertility with some chemo-therapeutic agents sparing fertility whilst others are extremely toxic in this regard.
- v) **Age dependent affects.** In the female in particular, age has a profound affect on chemotherapy toxicity. Women administered chemotherapy under the age of 40 have a much higher chance of regaining the normal ovarian cycle whilst the majority of women over 40 administered toxic chemotherapy will be rendered menopausal by their treatment. Presumably part of the reason for this is the fact that the natural attrition rate of oocyte sees a large drop in oocyte numbers over age 40 and this corresponds with decreased live birth rates in fertility patients over the age of 40.
- vi) **Male versus female physiology.** The testes in the male are exquisitely sensitive to chemotherapy whereas, as has already been stated, the female is variable in terms of the tolerance to chemotherapy agents.

Detailed information regarding fertility effects of many chemotherapy regimes is lacking, but specific examples where chemotherapy effects on fertility are documented include: -

TOXIC EFFECTS OF COMMONLY USED CHEMOTHERAPEUTIC AGENTS ON THE TESTIS

AGENT	KNOWN EFFECT ON TESTIS
Cyclophosphamide	Severe
Nitrogen mustard	Severe
Procarbazine	Severe
Bleomycin	Moderate
Carboplatin	Moderate
Cisplatin	Moderate
Cytarabine	Moderate
Doxorubicin	Moderate
Etoposide	Moderate
Ifosfamide	Moderate
Thioguanine	Moderate
Vinblastine	Moderate
Vincristine	Moderate
Methotrexate	Minimal

-Effects are dose-dependent.

-Severe = Azoospermia shortly after treatment with less than 20% recovery of spermatogenesis.

-Moderate = possible azoospermia shortly after treatment with 20 -50% of patients recovering spermatogenesis.

-Minimal = possibility of transient azoospermia but more than 50% of patients recovering spermatogenesis.

TOXIC EFFECTS OF COMMONLY USED CHEMOTHERAPEUTIC AGENTS ON THE OVARY

- i) **CMF** (classical breast cancer regime) will render 71% of women over 40 years of age amenorrhoeic at 2 years.
- ii) **Adriamycin and cyclophosphamide** has a 38% ovarian failure rate in women aged over 40 years at 2 years post- chemotherapy.
- iii) **CHOP (6 cycles delivering 4,500mg/m² cyclophosphamide)** does not usually lead to permanent amenorrhoea in women under 40 years of age, but may lead to early menopause in older women.
- iv) **ABVD** used in the treatment of Hodgkins disease is significantly less toxic in terms of fertility than the older **MOPP** regime.
- v) **Bleomycin & doxorubicin** have minimal effects on fertility.
- vi) **Vinca alkaloids & antimetabolites** have very mild effects on fertility (**Methotrexate** very mild at 6gm. total dose).
- vii) **Taxanes** are not clearly defined in terms of their impact on fertility.

3). RADIOTHERAPY EFFECTS ON FERTILITY

Clearly radiotherapy can be administered as **external beam therapy**, or as **intra-cavity** treatments. In addition to this, radiotherapy can be given with **radical** curative intent or as **adjuvant** therapy often post operatively.

The direct effects of radiotherapy are **dose dependent** and are also dependent to the **field** applied to the individual. It is important to consider the effect of **scattered radiation** as well as **direct irradiation** when assessing likely effect on fertility. For example, although pelvic irradiation may not

directly hit the testes in the male patient, scatter of radiotherapy will occur from this area which may have an impact on fertility.

i) Female Patients

Radiotherapy affects on the female are dose dependant. The application of 6 gray to an ovary in a woman over 40 years of age will usually render them irreversibly infertile and menopausal. A dose of 6 gray to the ovary of a woman less 30 years of age is usually reversible, but ultimately, will bring the menopause forwards. Thus the female is not only concerned with issues regarded sterility but also to hormone production, as both seem to be equally affected by radiotherapy.

Although the uterus is relatively resistant to radiotherapy there is no doubt that uterine irradiation is harmful and even if fertility is conserved, uterine irradiation will result in poor implantation. This appears to be due to reduced uterine blood flow, which has been demonstrated to result in increased mid-trimester losses, pre-term labour and intrauterine growth retardation. The vagina is relatively radio-resistant however; irradiation of this organ carries with it the risk of loss of lubrication and stenosis, which may result in physical impairments to fertility as well as major psychosexual issues.

ii) Male Patients

In the male the effect of radiotherapy on fertility is also dose dependent. The application of greater than 6 gray to testes will result in irreversible sterility. At levels of 3.5 gray, sterility does occur, but this is reversible although commonly such recovery will take 18 to 24 months. Interestingly, the Leydig cells of the testes seem far more resistant to radiation affect and therefore testosterone production is usually not impaired in patients receiving even relatively high dosages of radiotherapy. In addition, libido and erection will usually remain normal in the male and it is sterility that is the main concern.

4. THE CHALLENGE FOR CHILDREN

Examination of the trends in Five Year Survival Rates for the commonest childhood malignancies reveal sustained improvements in cure rates. Over the twenty-five year period from 1964, the five year survival for acute lymphocytic lymphoma has risen from close to 0% to close to 70%, for non Hodgkins lymphoma has risen from approximately 20% to almost 80% and for Wilms-tumour has risen from 25% to about 90%. Even since that time, five year survival rates have continued to rise slowly for these common forms of childhood malignancy. Although the challenge for poor prognosis tumours such as neuroblastoma remains to improve survival, for other tumours the challenge of the future is to sustain improvements in cure rates and to minimise the late effects for curable tumours. Preservation of fertility remains of great importance in these young patients and awareness of services available to them may reduce the long-term morbidity of their cancer treatment.

i). Young Male Patients

a)Background

The testicle is responsible for spermatogenesis (the production of mature sperm). In addition to this, it carries out steroidogenesis (the production of steroid hormones including testosterone). Damage to the Leydig cells of the testis results in reduced testosterone production and an elevated luteinizing hormone levels (from the pituitary gland). Damage to the germinal epithelial of the testes results in elevated FSH levels (also from the pituitary gland), low inhibin B levels and impaired spermatogenesis.

As previously discussed, a radiation dose of greater than 1.2 gray to the germinal epithelium will result in permanent azoospermia. In the pre-pubertal male, irradiation greater than 20 gray to the Leydig cells of the testis will cause significant damage in terms of testosterone production but in the post-pubertal male a level of greater than 30 grays is required to cause this level of damage.

A study by Thomson A.B. et al examined male fertility after childhood cancer (treated with radiotherapy or chemotherapy) and examined semen analysis in long term cancer survivors (average of five years post treatment) compared with controls. In the control group (untreated) 85% of subjects had a normal semen analysis; approximately 10% had poor motility and 5% oligospermia. The findings were quite different in the cancer survivors group : 30% of patients had normal semen analysis, almost 30% had poor motility, 15% had oligospermia and over 20% had azoospermia. Of the subjects who actually produced spermatozoa, it was clear that the concentration of sperm produced was significantly less than that of the control group. An analysis of sperm DNA integrity as a measure of quality of sperm showed no significant difference between the control and the cancer survivor groups. Thus, it can be concluded that sub fertility associated with previous treatment of childhood cancer may be due to azoospermia or oligospermia where there is a significant reduction in sperm concentration but normal sperm quality.

b) Strategies for fertility preservation in young males undergoing treatment for cancer.

Sperm banking remains the obvious choice for males capable of producing a semen sample. Certainly sperm retrieval should be offered to patients in whom, the risk of infertility is high, but there is now a good evidence base to suggest that if the testicular volume is less than 10mls, it is very unlikely that the patient will demonstrate any significant spermatogenesis. Thus sperm retrieval should be limited to males where testicular volume is greater than 10mls and samples should ideally be produced by ejaculation. In the situation where young males are unable to ejaculate then rectal electro stimulation or testicular/epididymal aspiration can be successfully undertaken. Sperm banking can then be done with the expectation that the semen can be used at a later date. At present, the later use of stored sperm is likely to require assisted conception methods such as intracytoplasmic sperm injection (ICSI) to optimise the likelihood of successful fertilization.

c) The Question of Sperm Storage:

A number of questions are raised by the opportunity to provide sperm storage for young male cancer patients:

1. There is uncertainty as to who exactly will need it
2. Who will raise the issue of sperm storage with the patient?
3. Where will the patient produce sample for storage?
4. When, in relation to their treatment, should the patient produce a sample? Situations arise where a patient is too ill or indeed has to be treated so acutely that there is insufficient time to offer this option?
5. Is it appropriate to discuss the issue of sperm storage with a patient who is struggling to cope with their diagnosis and forthcoming treatment
6. What is the cost of storage of sperm?

At present there is a one year audit being undertaken of all 22 UK CCSG centres which is MREC and HFEA approved. Part One of the study looks at what if anything was discussed with respect to infertility with the cancer patient and what risk of infertility was given. Part two of the audit details information on the quality of material stored, how it was obtained and what was discussed. Results of this study should be available next year but pilot interviews with adolescent males by Glaser, Crawshaw et al have revealed a number of common themes. Patients strongly believe their choice is of paramount importance and they strongly feel the need for information relating to sperm storage. Many patients sought increased input on the significance of fertility preservation and stressed the importance of communication with professionals on this subject. In addition to this, a common theme was that patients felt extremely pressured about making decisions with respect to sperm storage in this setting.

ii) The Legal Aspects of Fertility Preservation Young Cancer Patients

At present in the United Kingdom, a young person greater than 16 years of age is presumed capable of giving valid consent for treatment and removal of gametes (under common law) and storage and use of these gametes (governed by the HFE Act of 1990). A young person less than 16 years of age is presumed not capable of giving consent for treatment, removal of gametes and/or storage and use of these gametes. However, cases do exist where patients less than 16 years of age have been able to demonstrate capacity to undertake valid consent for this. A further complication is that young people less than 16 years of age who are not deemed competent can rely on their parents to give consent for medical procedures that are deemed to be in their best interest. Unfortunately, parents are not allowed to give consent for the storage and use of gametes, and therefore **there is currently no option to preserve fertility in the pre-pubertal boy.**

Experimentation is underway looking at the storage and use of gonadal tissue from children and whilst this has major ethical issues, not least of which is consent (which is only valid if it is voluntarily obtained from an informed, competent person). Proxy consent can be undertaken in a therapeutic setting if it is deemed to be in the best interests of the patient, but the question

remains as to whether removal of gonadal tissue is actually fulfilling this criteria. The Human Fertilisation and Embryology Authority (HFEA) 1990 Act has jurisdiction over the storage and use of live human gametes and embryos created in vivo, and by definition a gamete is “reproductive cell with a haploid set of chromosomes that is able to take part in fertilisation with another of the opposite sex to form a zygote”. The implications of this Act mean that no licence is required to store gonadal tissue from pre-pubertal children because they do not contain gametes and therefore primordial follicles in the cortical strips of ovaries (which are not considered gametes) may be stored for girls whose parents consent on their child’s behalf because they believe that retrieval and storage of this tissue is in the girl’s best interests. Unfortunately the same does not apply to boys and although boys with Tanner Stage 2 or greater development may have tissue stored in accordance with the 1990 Act if they can give written informed consent, parents are not allowed on their child’s behalf in this setting.

5. FERTILITY PRESERVATION IN THE MALE CANCER PATIENT

Sperm banking remains the obvious choice for males capable of producing a semen sample. Other techniques previously discussed for young male patients can be applied to adult patients. (see section 4 i) b) above)

i) Practical Laboratory Issues for Sperm Banking:

A critical factors for male patients requiring sperm banking is the timing of production sample as it is essential that this occurs before chemo or radiotherapy is undertaken. Prescreening is required to ensure that patients are checked for Hepatitis B and C, HIV and CNV. (Although positive results will not preclude a patient from undertaking sperm storage, a positive result will determine the batching required for semen storage). Appropriate paperwork is then undertaken as required by the HFEA.

Patients are then required to attend the Reproductive Medicine Centre to produce a semen sample (ideally this should be three samples a few days apart). Samples are then stored in liquid nitrogen at minus 196 degrees centigrade in two separate locations indefinitely. Each sample undergoes under a standard diagnostic semen analysis and is assessed against standard criteria (WHO 2000):

- Volume greater than or equal to 2.0mls
- The liquifaction time within 60 minutes
- ph 7.2 or more
- sperm concentration of 20 million per ml
- total sperm count of 40 million or more
- motility of sperm greater than 50%
- sperm morphology at least 30% normal forms.

ii) Long term considerations

Approximately 50% of sperm stored will be lost during the preservation and storage process.

Most patients receive an annual letter from the Andrology Unit storing their semen to check that the patient wants the sample to be retained in storage. For patients to be eligible for semen storage they must be less than 55 years of age, they must be able to give informed consent for both storage, screening and the fate of the sperm. It is certainly feasible to store sperm for many years and, at present, patients are not charged for this facility but the issue of whether the NHS should be formally funding this remains unanswered.

6. FERTILITY PRESERVATION FOR FEMALE CANCER PATIENTS

i) Options for fertility conservation:

1. **Hormone protection by suppressing ovaries.** GnRH analogues have been utilised during chemotherapy to suppress ovarian cycling and induce a temporary medical menopause. The action of GnRH analogues is not clearly understood as primordial and primary follicles do not have GnRH receptors and it is possible that GnRH analogues preserve those follicles that have already initiated growth. Several studies in animals have suggested that protection may be offered by undertaking this manoeuvre and there is currently ongoing work to examine this. The Option Trial (Ovarian Protection Trial in Oestrogen Non- Responsive Premenopausal Breast Cancer Patients Receiving Adjuvant or Neo-Adjuvant Chemotherapy) for breast cancer looks at hormone suppression using GnRH analogues and progestogens and examines the impact of this on fertility. This is ongoing work but many women are choosing to use this approach off-trial.
2. **Ovarian transposition** (surgically removing ovaries out of an intended radiation field). Although this is certainly an option and can be undertaken using minimally invasive techniques it is an option that is rarely used with the possible exception of gynaecological cancers where at the time of primary surgery, a surgeon may elevate the ovaries above the pelvic brim to avoid irradiation during a direct pelvic field.
3. **Storage by cryopreservation of embryos, oocytes or ovarian tissue.** The choice of what tissue type should be preserved depends on the type of cancer, the patient's age and whether she has a partner. Often it is time however that is the limiting factor in this choice.

ii) Embryo Storage:

Embryo storage is ideal for an adult woman in a stable relationship as it is an established technique which has been available since the mid 1980s. IVF offers a success rate of approximately 25% per cycle and this is similar to the natural conception rate that is achievable by healthy couples without assisted reproductive techniques. It involves stimulated ovarian cycle using fertility drugs which results in high oestrogen levels, and certainly this raises concerns for some tumours such as breast cancers with oestrogen receptor positivity. It is still unclear what the risks of such techniques in terms of tumour progression or relapse in a hormone dependent cancer. Some groups have attempted to address this by using tamoxifen alone or in combination with standard IVF stimulation for women with breast cancer or endometrial cancer. Patient numbers are small and long-term studies are currently not available.

IVF stimulation takes a minimum of two to three weeks depending on a patient's menstrual cycle and could be anything up to five weeks. After stimulation of follicles to maturation an egg collection procedure is undertaken usually as a day case under sedation or a general anaesthetic where vaginal probe ultrasound is used to guide transvaginal collection of eggs. IVF is then undertaken to fertilise the patient's eggs with partner's sperm before freezing the embryo. At present there is no facility to use donor sperm for adult women trying to preserve reproductive potential whilst undertaking chemotherapy.

iii) Oocyte Storage:

This technique is suitable for adults and for older teenagers who do not have a current partner. It is important to realise that this is a new technique and success rates are low at present with perhaps only 5% success rates achievable per cycle. Clearly this figure may rise with improved techniques in the future but at present less than 100 pregnancies have been documented worldwide using this technique. The technique involves stimulation of mature eggs, harvesting of these eggs and then freezing them, which is technically very difficult. Stored eggs can later be thawed and using IVF techniques with ICSI. Oocytes are much more sensitive to damage from cryopreservation techniques than embryos (probably secondary to spindle damage). For younger patients oocyte storage may be an option as harvest techniques can include transabdominal ultrasound and laparoscopy for retrieval of eggs rather than subjecting the patient to transvaginal technique.

iv) Ovarian tissue storage:

This is a technique that can be used for adults and for children and it is very much experimental at the present time. Laparoscopy is required to undertake a biopsy of an ovary or to remove the whole ovary for preservation. (All cases of successful post-implantation pregnancy reported to date have utilised the whole ovary). It is therefore an invasive procedure under general anaesthetic and carries a mortality rate of 1 in 12,000. Tissue obtained is cut into thin sections and then cryopreserved with a relatively straightforward fashion. Fewer than 15 patients world-wide have had their thawed ovarian tissue re-implanted via either orthotopic or heterotopic transplantation. Until recently there had been no case reported of successful live birth after orthotopic transplantation of cryopreserved ovarian tissue. Donnes and Dolmans reported in The Lancet Journal 2004 a live birth after transplanting cryopreserved ovarian tissue back into the pelvis of a woman following treatment for Stage 4 non Hodgkins lymphoma and Meirou et al in 2005 reported a further live birth in another young woman who had also been treated for non-Hodgkins lymphoma.