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A fertile future?

Life after cancer in young men

'Preserving fertility may be less urgent than preserving life, and if the methods for doing so are not straightforward or readily available, they may not be utilized at this crucial time.'

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With increasing numbers of children and young people surviving cancer, attention is now focused not only on their quality of life after treatment, but also on their future reproductive choices. In this editorial, we discuss treatment options available to post-pubertal men with cancer wishing to preserve their fertility. We also explore decision-making around fertility preservation, by young, single men who may not previously have considered starting a family, and legal and ethical aspects of the potential of fertility preservation.

Increased survival rates after childhood cancer

Wallace *et al.* suggest that, by 2010, one in 715 people in the UK will have survived childhood cancer, owing largely to recent advances in treatment, most of which carry implications for future fertility [1]. Testicular germ cell tumors, although rare (7.5 per 100,000 men in UK per year), are the most common malignancy diagnosed in men aged between 20 and 30 years, which represents approximately 1400 new cases per year in the UK [101]. The peak incidence for teratomas is 25 years, and 35 years for seminomas. In view of these encouraging survival rates, increasingly attention is being drawn to chemotherapy-induced subfertility [2]. Pacey points out that fertility can either be directly (gonadal) or in-directly affected in the context of pituitary malfunction [3], and comparative studies suggest the cytotoxic effect of chemotherapy on spermatogenesis is predominately dose specific [2–4].

Testicular cancer and Hodgkin's disease have been known to have a direct effect on the testes; therefore, these patients often cryopreserve abnormal samples [5]. Schroder *et al.* report gonadal toxicity as an important adverse effect of chemotherapy and radiotherapy [4], but argue that assessment or prediction of individual risk of infertility or gonadal failure is inaccurate at present. This is supported by Naysmith *et al.* [6], but in cases where testicular malignancy was treated with radiotherapy or alkylating chemotherapy agents, there was a reduction in semen concentration. Therefore, knowledge of preventive strategies to improve post-treatment fertility is an important issue [4,7]. It is also known that some men will retain all or most of their fertility following treatment and go on to father spontaneous pregnancies [8], while others will experience impaired fertility or azoospermia and will need to make use of their stored samples along with assisted conception.

Reproductive choice and the ability to have children is a normal expectation of life [9,102] and infertility can be a devastating side effect of cancer treatment [3,10]. Nevertheless, when faced with the diagnosis of malignancy, the concern of most patients and their families is to embark on therapy, with curative potential, as soon as possible [102]. Preserving fertility may be less urgent than preserving life, and if the methods for doing so are not straightforward or readily available, they may not be utilized at this crucial time. This editorial focuses on the future reproductive

choices and treatment options available to post-pubertal men with cancer, because data on fertility preservation and future reproductive treatments for women remain limited [3,7].

Methods of fertility preservation

Alongside higher survival rates following effective treatment of cancer [11], recent advances in reproductive medicine have resulted in new fertility preservation techniques for men [12–14]. Techniques for semen cryopreservation are now well established and rely largely on the availability and multidisciplinary awareness of andrology services [3]. For young men, whether in a stable relationship or not, it is crucial that semen cryopreservation is timely if they are to achieve their future reproductive potential and, perhaps more importantly, prevent delay in the start of chemo- or radiotherapy.

Assisted reproductive technology

As few data are available on the natural reproductive potential of cancer survivors [3,15], this review discusses reproductive choices in the context of the assisted reproductive technologies (ART). Until the late 1980s, intrauterine insemination using donor sperm (IUI/DI) or adoption were the only choices available to couples with severe male factor infertility [16], but it is now possible for couples to fulfill their reproductive potential with very few motile sperm. As a general guide, the overall concentration (number) of sperm available determines the most appropriate method of ART [17].

The process of IUI is the least invasive ART available, but requires the normal criteria for semen quality post-thaw [18]. This technique involves the insertion of a thawed and prepared semen sample directly into the female uterus around the time of ovulation (either timed naturally or tracked by means of serum luteinising hormone and estradiol assays). It is, however, dependent on normal tubal status in the female partner.

ICSI (which involves the injection of a single sperm into the cytoplasm of the oocyte), has been available in the UK since 1992. Unlike conventional *in vitro* fertilization (IVF), it can be used where there is a relatively low sperm concentration.

ICSI offers reproductive hope to men with severe oligo- or azoospermia (subsequently obtained from the testes). In men with chromosomal or genetic causes of infertility, there are concerns that the actual process of selecting a single sperm, immobilizing it by removing its tail and injecting it through the zona pellucida of the oocyte may lead to potential inheritance of Y-chromosome defects by the male offspring [19]. By comparison, there does not appear to be any increased incidence of genetic disease in the offspring of cancer survivors in relation to the oncology treatment, which has the potential to produce mutations [3].

The sperm for fertility treatment can be obtained from different sources: the ejaculate or, in the event of the inability of a post-pubertal male to masturbate, a sample directly from the

testes, epididymis or vas deferens by surgical aspiration techniques. As discussed by Pacey, the reproductive assessment and choices available to cancer survivors depend on pre-existing fertility and/or medical conditions on completion of chemo- or radiotherapy [3].

Microepididymal sperm aspiration

This sperm extraction technique involves the insertion of a needle into the epididymal region of the testes where sperm are retrieved directly. It is important to bear in mind that younger (peripubertal) men will have a reduced level of sexual awareness [3], and it is not uncommon for young men recently diagnosed with cancer to experience fear and anxiety, which may inadvertently affect their ability to produce a semen sample 'to order', and these techniques may be of use in this context. Microepididymal sperm aspiration (MESA) is not considered appropriate in cases where men are rendered azoospermic after chemotherapy, where there is no sperm production at all.

Reproductive decision-making

The ability to retain reproductive potential is a critical determinant of quality of life in young male and female cancer survivors [7,17], and many of them are very concerned at the prospect of losing their fertility as a result of treatment [20]. In many of those diagnosed with cancer, the immediate emphasis is on their cancer treatment, with little time available to discuss its

impact on future fertility and their options for fertility preservation. Crawshaw and Sloper found that in the presence of possible or actual fertility impairment following cancer treatment in young men and women, what proved important was having choices, preserving fertility and communication with professionals and members of the family [102]. They wanted the choice of having a parent present and involved in decision-making, rather than having choices made on their behalf.

Geographical location and the availability of andrology and ART services may well impact on the underutilization of sperm cryobanking. Where services are available, it is not clear whether young people are given the information, but unable to retain it in their heightened emotional state, or whether they are not actually informed. Tournaye suggests that lack of awareness on the part of both oncologists and male cancer patients is a major barrier to preservation of reproductive potential [12]. It was reported very recently that young men found producing sperm samples at this critical time extremely difficult [103]. They wanted directions about where to leave a sample, reassurance that it would be dealt with and an opportunity to view it through the microscope. For many, this was the first time they had experienced sitting in a wheelchair, and perhaps a frightening preview of what might be to come.

However, more recently, there appears to be an increased awareness and utilization of sperm banking, coinciding with the advent of ICSI. ICSI's success using either fresh or frozen samples has meant that there is now a lower threshold for cryobanking sperm [21].

Current strategy for fertility services

In light of improved survival rates in young people with cancer, quality of life and reproductive health choices have become a priority area for the British Fertility Society (BFS). Between December 2000 and March 2002, the BFS convened a multidisciplinary working group to define a reproductive service framework for cancer survivors. This group concluded that further research into fertility preservation is required and highlighted the need for multidisciplinary communication in order that survivors of cancer might optimize their reproductive potential [22].

The National Institute for Health and Clinical Excellence in partnership with the UK Department of Health has made recommendations to the National Health Service (NHS) about how services should be organized and integrated to improve the potential outcome for patients [104]. Their effectiveness is apparent in the increased uptake of semen cryobanking prior to treatment [23].

Despite these advances, the future reproductive needs of young cancer survivors could be addressed better [7,105]. Sperm banking (which has been available since 1978) and oocyte cryopreservation (egg freezing) still appear to be underutilized [14]. Although there is no evidence to suggest that future fertility is not discussed, issues relating to sexuality remain among the most poorly addressed in cancer care, possibly owing to lack of knowledge and expertise, although there may be other reasons, such as embarrassment [24].

Freedom of choice: ethical & legal issues

The WHO is committed to ensuring that individuals have the capability to reproduce and the freedom to decide if, when and how often to do so [25]. Implicit in this right is information about, and access to, safe, effective, affordable and acceptable methods of fertility treatment [26]. The Human Fertility and Embryology Authority (HFEA), which regulates assisted reproduction clinics in the UK, also regulates the storage of sperm prior to men embarking on treatment that may impair their fertility, such as radiotherapy or chemotherapy. Where men choose to cryopreserve sperm, the consent form has been designed to allow long-term storage of sperm (up until their 55th birthday) in accordance with the criteria set out in the Code of Practice [106,107]. Prior to 2007, in cases involving the posthumous use of cryopreserved sperm, the law did not permit the deceased male to be named as the father on the birth certificate. More recently, the two Houses of Parliament established a Joint Committee on the Human Tissue and Embryos (Draft) Bill (Cm 7087), which was published by the Government on

17 May 2007. If passed by the scrutiny committee, the Act will amend the law to allow a deceased man to be recorded in the birth register as the father, and all subsequent children to be recognized as legal offspring of the deceased [108].

Awareness of the need for sensitivity and multidisciplinary communication is paramount for clinics when contacting patients after semen cryostorage, as some could be terminally ill and others may not have survived the cancer. There are additional ethical considerations in cases where the patient may be a minor and, in the context of informed consent, allows for direct representation. The HFEA Code of Practice states that parents cannot consent on behalf of their children to the cryopreservation or use of their sperm, or to the creation, storage or use thereafter of embryos created using their sperm [107]. The referring consultant must therefore be absolutely sure that the minor has sufficient understanding and is Gillick competent to give informed consent for gamete storage under the assessment of sexual maturity.

The reasons for the intention to preserve fertility must be morally justifiable. Implications counseling at the time of gamete storage must take into consideration possible scenarios about a future the patient may not have considered [27]. There are clearly ethical difficulties, not only in the consenting process, but in attempting to bring together different disciplines of medicine and legislation in the context of sperm cryopreservation for male adolescents [28].

Unfortunately, the European Union Tissue and Cells Directive, which comes into force in September 2007, may have a detrimental effect on existing facilities for cryopreservation that cannot afford to comply with "a harmonized regulatory framework to ensure the quality and safety of tissues and cells intended for transplantation and other human applications" [109]. Given that time is of the essence from diagnosis to semen cryostorage and treatment, the additional costs incurred by the directive may seem reasonable and justified to the policy makers, but not represent good value to the patient in the context of locally available cryopreservation services [109].

Five-year view

By 2010, one in 715 people in the UK will have survived childhood cancer, owing largely to recent advances in treatment, most of which carry implications for future fertility. Techniques for sperm banking are already well established; however, for women, techniques for fertility preservation need to be refined. The potential of stem cell research may lead to *in vitro* maturation of gametes, xenotransplantation of reproductive tissues and the creation of artificial gametes (which is indeed controversial). It is likely, however, that these advances will be available within the next 10 years, as scientists move to gain public support for creating human/animal embryos that may have the potential to investigate how some cancers are able to migrate elsewhere in the body, and improve the treatment of infertility.

Young men will continue to be diagnosed with cancer and population changes, improved prognosis of certain cancers with increased numbers of cancer survivors and advances in reproductive technologies suggest that the number of patients requiring preservation of gametes for future fertility will

increase dramatically over the next 20 years, presenting a huge challenge to the NHS. Existing evidence that patients are not using the facilities available for preserving fertility, and may be unaware of them suggests that health professionals may not be optimizing these patients' reproductive choices.

Key issues

- The diagnosis of cancer in the young male is a stressful life event with short- and long-term implications for future fertility and the psychological well-being of those affected.
- Many young men diagnosed with cancer may not realize their full reproductive potential due to a lack of awareness of the provision for sperm banking, the consequences of which may have long-term psychological effects.
- Techniques for banking sperm are now well established; however, the impact of the European Tissue and Cells Directive (EUTD, 2004) may result in smaller clinics being unable to deliver this service.
- Effective and timely communication between healthcare professionals involved at the time of diagnosis of cancer in young males is crucial for the preservation of future fertility.

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