Focus on Fertility Preservation

Fertility preservation techniques: laboratory and clinical progress and current issues

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Abstract

Human fertility is dependent on maturation of germ cells through meiosis and their association with supporting cells, which in the female are also the source of sex steroids. These processes are sensitive to both chemotherapy and radiotherapy thus can be damaged by anti-cancer treatments. The uterus is also sensitive to radiotherapy. Our understanding of and the ability to manipulate fertility has increased together with survival rates from many cancers, particularly those affecting children, younger men, and women. The growth of interest in fertility preservation for cancer patients is a natural union of these two fields. Sperm banking has been available for many years, and is a recognized and evidence-based option for men that should be available to all. Options for women and pre-pubertal boys and girls are, however, more experimental, other than for women of committing oocytes to fertilization and cryopreservation as embryos. This Focus Issue of *Reproduction* aims to address the current status of some of the clinical and laboratory aspects of this burgeoning subspecialty to highlight not only areas of progress but also areas of uncertainty where future developments are required to allow the provision of accurate information, and safe and effective treatments.

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Fertility preservation is a rapidly expanding area both in the laboratory and in clinical practice. Much of this emerging interest reflects the greatly improved survival rates of young men and women with malignant disease, and indeed this has been one of the major success stories of medicine over the last couple of decades. Increasingly, the emphasis is on improved quality as well as quantity of survival and naturally for many the prospect of losing one's fertility is of major importance. In both the United States and United Kingdom working parties organized by relevant professional organizations have recently produced comprehensive reports discussing the impact of cancer therapies on reproductive function and the current status of produce to the management of this problem (Lee *et al.* 2006, Report of a Working Party of the Royal College of Physicians, Royal College of Radiologists and Royal College of Obstetricians and Gynecologists 2007). In this issue of *Reproduction*, we bring together a series of articles to consider the state of the art of fertility preservation and highlight some of the outstanding clinical and laboratory aspects of this field, particularly areas of clinical uncertainty and where basic science developments are required before treatments that are theoretically very promising can be introduced into practice.

The explosion of interest can be dated back to the demonstration by Roger Gosden, David Baird and

colleagues that ovarian function and fertility could be restored in sheep following removal and cryopreservation of ovarian tissue with subsequent replacement into the pelvis (Gosden *et al.* 1994), albeit at the cost of the loss of most of the follicles in the cryopreserved tissue (Baird *et al.* 1999). Fittingly, Gosden provides in this issue a scholarly account of the early and more recent history of ovarian transplantation (Gosden 2008). This has now been used successfully with a small number of babies born to women who have had ovarian tissue cryopreserved and later replaced. While these successes are enormously encouraging for patients and their physicians there remain considerable uncertainties regarding all aspects of this approach to fertility preservation, including selection of appropriate patients and the most appropriate surgical approaches in this situation. These and related clinical issues are reviewed (Anderson *et al.* 2008). A central problem is the paucity of accurate information as to the degree of gonadotoxicity of chemotherapy regimens that develop and change rapidly. Our ability to assess the effects on gonadal function has been greatly enhanced by the development of new markers of the number of small follicles in women (i.e., anti Müllerian hormone; Anderson *et al.* 2006) and endocrine markers of spermatogenesis in men (i.e., inhibin B; van Beek *et al.* 2007). It is hoped that the

demonstration that ovarian tissue cryopreservation can be successful and of increased success rates with oocyte cryopreservation/vitrification (Gook & Edgar 2007) will encourage the collaborations needed between oncologists and reproductive specialists to investigate and develop these techniques further. Particularly pertinent is the application of this approach to children, and the need to consider the ethical aspects of children undergoing procedures that remain experimental and of uncertain benefit at the time of high emotional tension and vulnerability for them and their parents. It is well recognized that few men return to use cryopreserved sperm, although the reasons for this (e.g., how many retain their fertility) is less clear. The same may prove true for women and this is more important when gamete storage has required invasive surgery or drug treatment, and may have delayed anti-cancer treatments.

Complimenting these clinical issues is a comprehensive review of the current status of *in vitro* follicular maturation (Picton *et al.* 2008). This article gives a full analysis of progress and problems in the development of multi-stage techniques to support follicular growth from the primordial stage through the antral stages and subsequent *in vitro* maturation of oocytes. Mice have been successfully born using fetal ovary as a starting point and there are clear advances in early human follicle culture (Telfer *et al.* 2008), but Picton *et al.* highlight the many issues that remain before this can be used safely and effectively in clinical practice, including the major concerns regarding epigenetic modifications of the oocyte genome which may occur in culture.

Prevention is always better than cure, and Meistrich & Shetty review the issue of gonadal protection from chemotherapy and radiotherapy (Meistrich & Shetty 2008). While the rodent studies have led to valuable insights into the developmental regulation of testicular stem cells, the application of this to patients is unclear. However, the well-recognized observation that occasionally men can show very late restoration of spermatogenesis many years after chemotherapy suggests that when some spermatogonia survive they can later repopulate the seminiferous epithelium, and better understanding of the regulation of this process may be of considerable benefit to many men. The concept of gonadal protection remains very attractive with many patients (especially women) already treated with GNRH analogues prior to chemotherapy despite an absence of good evidence that this is of benefit (Blumenfeld 2007). High quality randomized studies are currently underway and it is hoped that they will provide clear data that will be of immediate clinical relevance.

While sperm storage is an established option for men and post-pubertal boys, options for pre-pubertal boys remain experimental. Considerable progress has been made, however, in establishing methods for somatic gonadal stem cell recovery from tissue for storage and possible re-implantation, and storage of testicular tissue

for subsequent culture and *in vitro* spermatogenesis, as reviewed by Ehmcke & Schlatt (2008). Such studies will also contribute to our basic understanding of the biology of the male gamete, and disorders of spermatogenesis.

There are many other exciting developments in reproductive biology at present of relevance to fertility preservation that are not covered in this Issue as they are at the early stages of understanding. These include the possibility of developing functional gametes from embryonic stem cells (Hubner *et al.* 2003, Nayernia *et al.* 2006), and potentially in the future from induced pluripotent cells (Takahashi *et al.* 2007). The clinical use of artificial gametes is some way off and is likely to involve considerable public debate and legislative activity, but with an increasing number of the young men and women cured of their cancer but sterilized by the treatment, it is important that this approach is given full consideration. The possibility that the ovary may have regenerative capacity has also attracted considerable debate in the last few years (Johnson *et al.* 2005, Telfer *et al.* 2005): at present many remain uncertain about this, although in this as yet embryonic era of regenerative medicine, knowledge derived from the regeneration of ageing heart, brain, and bones may be transferable to the reproductive system.

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