Preserving the reproductive potential of men and boys with cancer: current concepts and future prospects

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The introduction of ICSI has totally changed the reproductive prospects for boys and men who are treated for cancer. With post-pubertal boys and adult men, semen cryopreservation should be offered to every patient undergoing a cancer treatment since preservation of fertility cannot be guaranteed for an individual patient and treatment may shift to a more sterilizing regimen. In the ICSI era, all semen samples, even those containing only a few motile sperm, should be accepted for cryopreservation. Patients who are azoospermic at the time cancer is diagnosed may be offered testicular sperm extraction and cryopreservation of testicular tissue. With pre-pubertal boys, no prevention of sterility by sperm banking is possible since no active spermatogenesis is present. However, in the next decade, prevention of sterility in childhood cancer survivors will become a major challenge for reproductive medicine. In theory, testicular stem cell banking is the only way of preserving the future fertility of boys undergoing a sterilizing chemotherapy. In animal models, testicular stem cell transplantation has proved to be effective; however, it remains to be shown that this technique is clinically efficient as well, especially when frozen–thawed cells are to be transplanted. Malignancy recurrence prevention is an important prerequisite for any clinical application of testicular stem cell transplantation. Although still at the experimental stage, cryobanking of testicular tissue from pre-pubertal boys may now be considered an acceptable strategy.

Key words: cancer/cryopreservation/male fertility/stem cell/transplantation

From insemination to ICSI

Depending on the underlying disease, the age of the oncological patient, the type of therapeutic agent used to treat the cancer, the cumulative doses used and the duration of the treatment, 10–100% of surviving cancer patients will show reduced semen parameters after their cure. An average of 15–30% of cured cancer patients remain sterile in the long term (Schrader et al., 2001).

While many oncologists now tend to use less gonadotoxic treatments, semen cryopreservation should always be offered to each cancer patient since recovery of spermatogenesis cannot be guaranteed for the individual patient, because of important interindividual variances or because a therapeutic regimen may be started with limited gonadotoxicity, but eventually a more gonadotoxic therapy may be indicated because of treatment failure. In France, where the CECOS network of semen banks is well organized, it was estimated that 57% of Hodgkin patients and only 21% of patients with testicular cancer cryopreserved their semen before cancer treatment (Bastit and Bisson, 1989). Although it is generally assumed that men treated for testicular cancer have a better prognosis to preserve their progenitive potential, a recent large multicentre study showed that about one out of three treated patients had difficulties impregnating their partner, especially after radiotherapy (Huyghe et al., 2004).

Early reports on semen banking for oncological patients focused on the fact that few patients had semen samples compatible with successful cryopreservation in view of artificial insemination (Bracken and Smith, 1980; Sanger et al., 1980; Waxman, 1985). When the post-thaw semen analysis showed <40% motility and when the sperm density was <20 × 10^6 sperm per ml, cryopreservation of the semen of oncological patients was considered pointless because the chances of conception after treatment would be unacceptably low. Furthermore, most reports on artificial insemination showed that even though the pre-freeze sperm quality met the above criteria, pregnancy rates remained very poor (Hendry et al., 1983; Scammell et al., 1985). As a result, even today, many oncologists consider semen storage for cancer patients an inefficient, expensive and time-consuming strategy.
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However, with the introduction of more sophisticated techniques of assisted reproduction, such as IVF and ICSI, this view has become completely obsolete. The authors, who were indirectly responsible for the fact that for >10 years few cancer patients had been encouraged or allowed to bank their semen, eventually changed their minds and agreed that ‘semen banking should be offered as a viable option for any male cancer patient who has any motile sperm and is considering the possibility of having future children’ (Sanger et al., 1992). Thanks to the introduction of ICSI, cured cancer patients can now father children who are genetically their own, even with the poorest semen samples (Chen et al., 1996; Hallak et al., 1998; Lass et al., 1998; Naysmith et al., 1998; Tournaye, 2000; Ginsburg et al., 2001; Horne et al., 2001).

Yet, even now oncologists are not aware of the evolution of the techniques for assisted reproduction: a questionnaire sent to oncologists in Minnesota showed that 74% of the responding oncologists were unaware of recent advances in assisted reproduction and did not know about the existence of ICSI (Zapzalka et al., 1999). A recent Irish survey corroborates these findings (Allen et al., 2003). In a survey in the UK conducted in academic oncology units, 68% of the responding units said that their male cancer patients did not receive adequate information about their fertility and the preservation of their reproductive potential. Furthermore, only 9% of oncological units surveyed about cryobanking semen in the UK have information leaflets available (Bazeos et al., 1999).

Thus, there is a risk that patients undergoing potentially sterilizing cancer treatment are not appropriately counselled about their future fertility. So, although assisted reproductive technology can currently successfully preserve the reproductive capacity of many oncological patients, oncologists and their patients are still unaware of its real possibilities. This lack of awareness may be a major limiting factor in the cryostorage of semen of male cancer patients.

But even if properly counselled, not all patients will eventually bank semen before their treatment. One study reported that only 42% of appropriately counselled patients did bank their semen to counter sterility (Kliesch et al., 1997), while another recent study reported a value of 54% (Rousillon et al., 1999).

What should we bank?

In the ICSI era, almost any semen sample, even when it contains only a few motile sperm, may be considered for cryobanking.

Semen cryopreservation should preferentially be done before any treatment has started. Yet, many cancer patients are referred only when the final diagnosis of their disease is made and when little time remains to bank semen. Urgency to initiate chemotherapy is a major deciding factor for oncologists for referring their patients for cryobanking semen (Zapzalka et al., 1999). But again, one single semen sample, even of limited quality, is sufficient to perform several ICSI cycles. In our experience, after ICSI, redundant frozen–thawed sperm may even be re-frozen for later use without jeopardizing ICSI outcome. Therefore, cryostoring even a single semen sample is useful, and urgency for starting chemotherapy has become an unlikely excuse.

Most patients will develop azoospermia 2–3 months after starting chemotherapy (Schrader et al., 2001). Cryobanking semen during these first months of chemotherapy has been advocated as a means for overcoming the urgency problem (Carson et al., 1991). However, chemotherapy may induce genetic abnormalities in both the short and long term. Both the human sperm–hamster egg cytogenetic technique and fluorescence in situ hybridization (FISH) studies have indicated that chemotherapy and radiotherapy may induce both short-term (Rousseaux et al., 1993; Montei et al., 1997; Robbins et al., 1997) and long-term (Genesca et al., 1990; Brandriff et al., 1994; Foresta et al., 2000) chromosomal aneuploidy. In the long term, mutations too have been reported in sperm from patients who were treated by chemotherapy (Meistrich et al., 1985; Zheng et al., 2000). A recent paper reports that 33 out of 164 patients (20%) who banked their semen were only referred after starting their cancer treatment (Chung et al., 2004). But even before treatment, patients with malignancies may present higher aneuploidy rates in their sperm (Fait et al., 2001) and increased DNA damage (Kobayashi et al., 2001).

Given the absence of any clinical evidence of chromosomal abnormalities in offspring born from men undergoing chemotherapy or men who had chemotherapy, even patients who already started their cancer treatment should be offered cryobanking. Additionally, in order to control for aneuploidy, preimplantation genetic diagnosis (PGD) may be suggested whenever assisted reproduction is performed using sperm banked during chemotherapy.

Patients may be azoospermic at the moment of diagnosing cancer. This may be the result of a spermatogenic depression due to factors related to the malignancy (Berthelsen and Skakkebaek, 1983). Azoospermia may be encountered especially in patients with testicular cancer. One study reported an azoospermia rate of 18% in 147 patients referred for pre-treatment semen cryostorage (Fossa et al., 1989). A more recent study dealing with various types of cancer reports an azoospermia rate of 17.3% (40/231) (Lass et al., 1998). Figures on testicular cancer patients from CECOS centres in France show lower azoospermia prevalences: 6.2% in Paris (reported over a 20 year period) (Auger et al., 2000) and 3.1% in Toulouse (Mansat et al., 1989). In a series of 33 patients with lymphoma, five (15%) were azoospermic (Tal et al., 2000); however, in another report on 23 patients, none were azoospermic (Pryzant et al., 1993). Although these values may be underestimated because of selection bias, they stress again that a significant proportion of cancer patients may not be offered semen cryopreservation. A recent study on a large population reported that 3.3% of patients (31/930) referred for cryostorage were azoospermic (Kelleher et al., 2001).

Such azoospermic patients may be offered sperm recovery and banking before starting chemotherapy by vasal or epididymal sperm aspiration during orchietomy (Baniel and Sella, 2001) or testicular sperm extraction (TESE) (Rosenlund et al., 1998; Res et al., 2000; Kohn et al., 2001; Schrader et al., 2002).

Utilization of cryopreserved semen from oncological patients

A survey in the UK on the use of semen samples stored from 1977 to 1987 showed that only 133 out of 2219 men eventually used their cryopreserved semen (6%) (Milligan et al., 1989)—a number comparable to that reported by Kliesch et al. (1997)
who found that over an 8 year period, only 8% of patients used their semen for assisted reproduction. A recent French questionnaire reports that only one out of eight men who want to have children used their banked semen for assisted procreation (Rousillon et al., 1999). In the study by Lass et al. (1998), only six out of 191 men who had semen banked eventually had assisted reproduction treatment with their frozen gametes. Kelleher et al. (2001) reported that 64 out of 833 (7.7%) men used their cryostored semen to achieve a pregnancy. A recent American study reports a utilization rate of only 4.7% (Chung et al., 2004).

There are different reasons for not using the stored semen or even for discontinuing its storage. A questionnaire in the USA showed that 41% of patients discontinued storage because of recovery of fertility potential with paternity, 37% because of death, 14% because good sperm quality was regained and 7% because they did not want children (Hallak et al., 1998).

A questionnaire completed by cured testicular cancer patients revealed that 15 out of 76 wanted to have children (19.7%), and although they had semen banked, they did not request assisted reproduction treatment after a delay of ≥4 years (Lanfrey et al., 1997). Cured oncological patients may refrain from reproducing because they may be concerned about the adverse effects of cryostorage, the increased aneuploidy even before chemotherapy or even the heritability of their cancer. Finally, not being aware of new developments in assisted reproduction may also contribute to the under-utilization of stored semen (Allen et al., 2003). Here too, appropriate counselling after treatment may intensify the use of cryostored sperm after cure.

Assisted reproduction using sperm from oncological patients

Large prospective or even retrospective studies comparing the outcome of assisted reproduction with sperm from oncological patients are currently unavailable in the literature. In a retrospective review (Sanger et al., 1992), only 43 out of 191 couples (22.5%) conceived after artificial insemination using the husband’s frozen–thawed semen. However, in the same review, 10 out of 12 couples conceived after IVF. Thus compared to artificial insemination, IVF achieves higher success rates (Tournaye et al., 1993). However, many publications in this review are case reports with a successful outcome. But in our small consecutive case series on 11 cycles from five patients with Hodgkin’s disease, all fathered a child after conventional IVF (Tournaye et al., 1991). Nevertheless, only 31 out of 104 oocytes were fertilized (30%) and in two cycles a complete fertilization failure occurred. In both cycles post-thaw motility did not exceed 5%. Furthermore, ≥2 ml of cryostored semen had to be thawed in order to have enough sperm to allow conventional insemination in vitro.

Another, larger case series corroborates these findings (Khalifa et al., 1992): in two out of 12 cycles from 10 patients, no fertilization was obtained. Patients in whom no motility was observed post-thaw (n = 2) were offered subzonal insemination (SUZI) and although embryos were obtained, no pregnancies were obtained after embryo transfer. In a recent study by Kelleher et al. (2001), however, IVF was found to be less efficient than intrauterine insemination.

In contrast, ICSI should be far more successful than conventional IVF for obtaining fertilization in vitro when cryostored sperm from oncological patients are to be used. Nevertheless, the literature on ICSI using sperm from cured cancer patients is scarce.

Occasionally, case reports are published or ICSI cycles are mentioned in papers reporting on different assisted reproduction treatment methods using frozen–thawed semen from cured patients (Hakim et al., 1995; Chen et al., 1996; Ahuja et al., 1997; Hallak et al., 1998; Lass et al., 1998; Tournaye, 2000; Ginsburg et al., 2001).

The largest retrospective series reports on 64 patients who had either intrauterine insemination (n = 35 cycles), conventional IVF (n = 28 cycles) or ICSI (n = 22 cycles) depending on the semen quality. Yet, in order to obtain a pregnancy, a median of 8 (SEM 3) IUI cycles was required against 3 (SEM 1) for ICSI (Kelleher et al., 2001).

These results clearly show that all efforts to convince oncologists of the important advances in assisted reproductive technology should be continued. They must realize that only azoospermic semen samples are to be rejected for pre-treatment cryopreservation.

What can we offer when no semen was banked?

Many patients did not have had their semen stored before starting cancer treatment and became severely oligozoospermic or even azoospermic after their treatment.

Post-chemotherapy oligozoospermic patients may benefit from ICSI (Tournaye, 2000; Ginsburg et al., 2001). Many patients with testicular cancer experience anejaculation because of retroperitoneal lymph node dissection. Here, transrectal electroejaculation has proved successful in obtaining sperm for assisted reproductive technology (Hakim et al., 1995; Rosenlund et al., 1998).

Some patients with post-chemotherapy azoospermia may benefit from testicular sperm extraction (Tournaye, 2000; Chan et al., 2001; Damani et al., 2002).

In any case, patients willing to undergo ICSI after chemotherapy must be informed about the possible long-term adverse genetic effects of their treatment (see above). Because, to date, only anecdotal data are available in the literature, no valid conclusions as to the efficiency and safety of assisted reproductive technology in these patients can be drawn.

However, the few clinical data available on spontaneous conceptions after chemotherapy are consistent and do not suggest an increased risk of congenital anomalies in the children born from patients where pregnancy occurred during or after their father’s chemotherapy (Holmes and Holmes, 1978; Li et al., 1979; Blatt et al., 1980; Senturia and Peckham, 1990; Hawkins, 1991; Dodds et al., 1993; Nicholson and Byrne, 1993; Green et al., 1991, 1997).

Furthermore, new developments in assisted reproduction may be helpful: pre-implantation aneuploidy screening may ensure that embryos obtained with sperm collected during chemotherapy do not carry structural chromosomal anomalies.

Cancer in adolescents

While in adult male oncological patients semen banking is well accepted as a preventive strategy, the same is not true for...
adolescents. A study by Kliesch et al. (1996) demonstrated that adolescent patients, aged 14–17 years, are good candidates for semen banking. In a large series, Bahadur et al. reported that 86% of 238 boys of post-pubertal age up to 19 years old could produce a semen sample for cryostorage (Bahadur et al., 2002a). In four out of the remaining 33 boys, eventually sperm recovered from a urine sample was cryopreserved (Bahadur et al., 2002b). A study involving 45 male adolescents showed that for 20 of them (44.5%) semen cryopreservation was not performed because they were not judged as being mature enough to deliver a semen sample by masturbation. Another four boys failed to deliver a semen sample because of masturbation problems and, finally, for two boys semen was collected by alternative methods such as penile vibrostimulation or electroejaculation, both performed under general anaesthesia (Muller et al., 2000). Electroejaculation in adolescents may be an alternative to masturbation in order to obtain semen for cryostorage (Schmiegelow et al., 1998; Hovatta et al., 2001).

Pediatric patients: the reproductive challenge for the next decades

About one in every 600 children will develop cancer before the age of 15 years. In recent years, remarkable progress has been made in the treatment of cancer in infants and children and up to 75% of them can now be cured. Today, as a result of better treatment options, the cancer death rate in children has decreased more than that for any other age group. At present, one in 1000 adults in the age group of 20–30 years old is a childhood cancer survivor (Hawkins and Stevens, 1996), and it has been estimated that by 2010 this proportion will rise to one in 250 (Bleyer, 1999). From these figures it is evident that prevention of sterility in childhood cancer survivors will become a major challenge in reproductive medicine. When an adult man undergoes a sterilizing treatment or ejaculates sperm, the sperm can be frozen in order to circumvent sterility after his treatment. However, no such prevention is possible before puberty since no active spermatogenesis is present.

Many rodent studies have shown a protective effect of GnRH agonist treatment either alone (Ward et al., 1990) or in combination with androgens and estrogen (Meistrich et al., 1994) or anti-androgens (Kangasniemi et al., 1995). Despite these hopeful findings, little progress has been made in the human and most clinical pilot studies fail to show any benefit of hormonal protection against gonadal damage (Krause and Pfluger, 1989; Kreuser et al., 1993).

Given the above survival estimates, the preservation of the progerminative potential in boys will become an important challenge for fertility specialists. The storage of pre-pubertal testicular tissue is currently emerging as a potential solution (Schlatt, 1999; Aslam et al., 2000; Bahadur et al., 2000; Schlatt et al., 2000; Hovatta, 2001). After being cured, the frozen–thawed tissue may theoretically be transplanted (Schlatt, 1999; Schlatt et al., 2000), xenotransplanted (Honaramooz et al., 2002; Schlatt et al., 2003) or matured in vitro (Nagano et al., 1998; Feng et al., 2002). So far, the testicular stem cell transplantation has provided the most promising results in animal models, mostly murine models. Also, ethically, autologous testicular stem cell transplantation may be more acceptable than xenotransplantation strategies.

Testicular stem cell transplantation

A decade ago, it was demonstrated that spermatogenesis could be re-initiated after transplanting testicular stem cells (Brinster and Zimmermann, 1994): spermatagonia from pre-pubertal mice were injected into the seminiferous tubules of adult mice with a Sertoli cell-only syndrome induced by a cytotoxic treatment. Using a donor mouse with a transgenic marker (lacZ), Brinster and Zimmerman proved that the adult recipient mice produced sperm derived from the donor mice. It was also shown that the recipient mice could reproduce in vivo after transplantation and produce transgenic offspring (Brinster and Avarbock, 1994). Subsequently, these experiments were performed using stem cells that had been frozen and thawed (Avarbock et al., 1996).

Testicular stem cell banking and subsequent transplantation after thawing (autologous transplantation) could thus theoretically circumvent sterility induced by chemotherapy in pre-pubertal boys cured of cancer. To date, transplantation has only been successfully applied in animal models mainly for fundamental research purposes. Apart from the preservation of the fertility potential of pre-pubertal boys or even adult men, testicular stem cell transplantation has also been proposed as a means of treating male subfertility in adult men (Ögawa et al., 2000; Kanatsu-Shinohara et al., 2003).

However, any clinical application of this transplantation procedure requires not only a thorough ethical reflection (see Bahadur et al., 2000 for review), but also a critical assessment of the feasibility of the transplantation technique and an assessment of its safety regarding both normality of meiosis after cryopreserving and transplanting stem cells and the risks of transplanting carcinogenous cells into an otherwise cured patient.

Clinical application of testicular stem cell transplantation

To date, restoration of fertility after transplanting testicular stem cells has only been demonstrated in mice (Brinster and Avarbock, 1994) and rats (Hamra et al., 2002; Zhang et al., 2003).

Some years ago, human autologous transplantations of frozen–thawed testicular cell suspensions were performed in adults (Radford et al., 1999), but this application, which was proposed as an alternative to sperm banking, has not been reported to be successful so far. Most work has thus been performed in mice. From work carried out so far, it is clear that testicular stem cell transplantation is efficacious, both after transplantation of fresh suspensions (Brinster and Avarbock, 1994) or frozen–thawed suspensions (Kanatsu-Shinohara et al., 2003). We evaluated the fertilizing ability of sperm obtained after transplantation of fresh testicular stem cells in a mouse model (Goossens et al., 2003). After IVF, we found a lower fertilization rate in the transplanted group compared to controls, but after ICSI, the fertilization rate was comparable to control sperm. Although blind extrapolation of findings in the mouse to the human situation is impossible, e.g. because of differences in the stem cell population, differences in testicular anatomy or the risks involved, these findings show that any clinical application will need to be assessed for efficiency at a certain point, certainly if testicular germ cell banking is proposed as an
alternative to a long-established successful strategy such as sperm banking in men with active spermatogenesis.

Whereas in mouse models, several dissected donor testes are used for transplantation, in a clinical setting only a small testicular biopsy can be obtained. Because further scarring and fibrosis after chemotherapy of the remaining part of the testis may be anticipated, it may be acceptable to perform a unilateral orchectomy. But even then, one small pre-pubertal testis at the most can be removed. It has been estimated that in the mouse only 0.03% of testicular cells are stem cells (Tegelenbosch and De Rooij, 1993). However, this proportion is assumed to be higher in the human. In mice, spermatogonial enrichment can be obtained by surgically inducing cryptorchidism or by inducing vitamin A deficiency (McLean et al., 2002), but these approaches are not practicable in a clinical setting. Enrichment by magnetic cell sorting or fluorescence-activated cell sorting (FACS) has been shown to enrich the proportion of testicular stem cells in the mouse by seven and 166 times respectively (Shinohara et al., 2000). However, it remains to be shown which surface markers are expressed on human testicular stem cells in order to obtain enriched cell populations. The transfer technique itself has been the subject of further study (Schlatt, 1999; Brook et al., 2001). It has been shown that because of the anatomical differences between man and mouse, infusion under gravity pressure via multiple punctures into the rete testes may provide the best results in terms of filling the seminiferous tubules with a stem cell suspension. In order to reduce the backpressure from intratubular fluid secreted by the Sertoli cells, priming recipients with GnRH antagonists before infusion may be necessary as shown in non-human primate models (Schlatt, 1999).

Another important issue is the timing of the re-introduction of the testicular stem cells in the case of autologous transplantation. In mice it has been shown that transplanting frozen–thawed stem cell suspensions to pre-pubertal recipients was more successful than to adult recipients, especially after busulphan treatment (Kanatsu-Shinohara et al., 2003). In mice it has been shown that the functional capacity of the stem cells may be compromised by cryopreservation despite a good survival rate of the testicular cells, which was in contrast to another recent study reporting an improved post-thaw restoration of spermatogenesis (Kanatsu-Shinohara et al., 2003).

Cryostorage of testicular stem cells

An optimal cryopreservation protocol is another prerequisite for clinical application. In the mouse, testicular stem cells seem to survive simple freezing procedures much better than mature sperm (Avarbock et al., 1996; Nakagata, 2000). Yet, few data exist on the efficiency of cryopreservation of testicular stem cells. Brook et al. (2001) compared different cryopreservation protocols, but failed to show any effect of the cryoprotectant used on the survival of human testicular cells after cryopreservation. Hovatta (2001) reported on six different freezing and thawing protocols for both mouse and human testicular cell suspensions. Here, a slow-programmed protocol using dimethylsulphoxide with sucrose provided the best cell survival of isolated bovine type A spermatogonia (Izadyar et al., 2002). The frozen–thawed bovine spermatogonia retained their ability to proliferate in vitro and to survive for up to 3 months after xenotransplantation into a mouse testis.

In a stepwise comparative study, we evaluated different cryopreservation protocols for cell survival and restoration of spermatogenesis post-thaw (Fredericks et al., 2004). This study showed that the functional capacity of the stem cells may be compromised by cryopreservation despite a good survival rate of the testicular cells, which was in contrast to another recent study reporting an improved post-thaw restoration of spermatogenesis (Kanatsu-Shinohara et al., 2003).

Safety of testicular stem cell transplantation

Acute lymphoblastic leukaemia (ALL) is the most common type of childhood cancer, representing about one-third of all cancers in children <15 years of age. Testicular leukaemic infiltration can be expected, and if remaining undiagnosed when treatment ends, it may adversely affect treatment outcome (Heaney et al., 1983).

In a rat model, it has been shown that testicular cell suspensions from T-cell leukaemic donor rats can induce testicular leukaemia in recipients undergoing testicular transplantation of fresh or frozen–thawed donor samples (Jahnukainen et al., 2001). In theory, however, testicular stem cell transplantation can introduce a risk of cancer recurrence in every metastatic childhood cancer because of contamination of the cell suspensions with carcinogenic cells contained in the testicular blood vessels. In the mouse, recurrence of malignancy has also been reported after ovarian tissue grafting (Shaw et al., 1996).

In order to circumvent the problem of malignant contamination, cell sorting may be a strategy. At present, FACS has been shown to enrich testicular stem cells, but it has still to be shown that malignant cells can be negatively sorted from the cell suspensions preventing any contamination by malignant cells.

Developing human testicular stem cells to maturity in surrogate animals could be another strategy (Sofikitis et al., 2003). So far, preliminary experiments on xenogeneic transplantation have not been invariably successful. Transplanting of the stem cells from hamsters, rabbits and dogs has failed to initiate spermatogenesis in recipient mice, probably because the phylogenetic gap between these species is too wide (Dobrinski et al., 1999). Although, in 1999, Sofikitis reported complete spermatogenesis after xenotransplantation of human spermatogonia into mice (Holmes, 1999), other researchers reported that xenologous transplantation from human to mouse (Reis et al., 2000) or primate to mouse (Nagano et al., 2001, 2002) failed to initiate spermatogenesis.

Xenografting may be an alternative way of circumventing malignant contamination. In a recent report, non-human testicular xenografts were shown to support spermatogenesis in immunity-deficient mice (Honaramooz et al., 2002). Although this approach may raise ethical concerns, one day it may provide an efficient means of preventing malignancies when attempting reproduction in certain childhood cancer survivors.

Apart from the malignant contamination, other theoretical safety issues may arise. When xenotransplantation or
xenografting techniques are to be used, there is a theoretical risk of viral transmission or transmission of prions from the recipient to the human cells or tissue, and even when assisted reproduction is performed, vertical transmission to the oocyte remains a possibility (Lacey and Dealler, 1994; Patience et al., 1998).

When assisted reproduction is to be used as a means of reproducing after testicular stem cell transplantation, there is a theoretical but yet unproven risk that chromosomally abnormal gametes or gametes with deficient imprinting may be successfully used to obtain fertilization and generate embryos.

Conclusion

With cancer being treated more successfully, the focus of the treatment as a whole will shift more and more towards the quality of life after treatment. In adults and adolescents, semen banking or cryopreservation of testicular tissue before any treatment are valuable preventive measures in combination with techniques of assisted reproduction and ICSI especially. It is mainly a lack of awareness on the part of both oncologists and male cancer patients that limits the preservation of the progenitive potential of the latter.

Although still purely experimental at this stage, testicular stem cell transplantation may provide an adequate solution to preserve the progenitive capacity of pre-pubertal boys. Although still surrounded by complex ethical issues, cryobanking of testicular tissue from pre-pubertal boys may now be considered an acceptable strategy, analogous to cryobanking of ovarian cortex in young girls. However, in contrast to girls, in boys, stem cells are the target of storage, which represents an important difference in terms of potential future applications for preserving fertility.

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