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CLINICAL REVIEW

Preservation of fertility in adults and children diagnosed with cancer

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In the United Kingdom each year 11 000 patients aged 15-40 years are diagnosed with cancer, and more than half of them will live for more than five years.[1,2] Patients want quality of life, including the ability to have a family, and many request advice on fertility preservation. This review describes the fertility preservation techniques available and recent recommendations from the UK and the United States.[3-5]

Why should oncology patients consider fertility preservation?

Chemotherapy and radiotherapy reduce the number of germ cells within the ovary and decrease testicular spermatogenesis; this reduction is related to the dose, agent used, and age at treatment. In addition, patients are at risk of permanent gonadal failure.[3,4] The persistence of menstrual cycles after treatment does not preclude ovarian damage, and the preservation of testosterone production does not confirm the preservation of spermatogenesis.

Who should be referred to discuss fertility preservation options?

UK and American Society of Clinical Oncology (ASCO) guidelines recommend that the implications of oncological treatment for fertility are discussed with patients.[3,5] The need to refer for fertility advice will depend on the patient's age, disease, prognosis, and time interval before treatment. Many patients seek advice from their general practitioner, oncologist, and allied health professionals, but evidence from several observational studies indicates that many do not receive adequate informed advice.[6]

SOURCES AND SELECTION CRITERIA

We searched Medline and the Cochrane library using the keywords "cancer and fertility", "chemotherapy and fertility and radiotherapy and fertility", "fertility preservation", "ovarian transposition", "oocyte freezing/cryopreservation", "sperm freezing/cryopreservation". We also used information from the National Institute for Health and Clinical Excellence; the Royal College of Physicians, Royal College of Radiologists, and Royal College of Obstetricians and Gynaecologists working party; and the American Society of Clinical Oncology.

What options are available for men?

As a result of the systemic effects of cancer, semen quality is often poor, and azoospermia is often present in Hodgkin's lymphoma and testicular cancer before chemotherapy.[4] The sperm count is lowest in the six months after treatment and may need two years to recover.[7] The risk of producing chromosomally abnormal sperm is highest in the few weeks after completion of chemotherapy,[7] so men should wait six months before conception is attempted. Hormonal suppression has not been shown to help reduce testicular damage caused by chemotherapy.[3]

Men and adolescent boys preparing for chemotherapy should be offered semen cryostorage, which has been shown to be effective in many small observational studies[8-10] and is recommended by the National Institute for Health and Clinical Excellence (NICE) and ASCO.[3,5] Large prospective studies have found no increase in abnormalities for children born after semen cryopreservation,[11,12] although sperm that have been frozen may be less effective in assisted reproduction.[13]

It is difficult to discuss the production of semen samples with adolescent boys and we have no reliable method to determine if they are able to produce a sample. Anecdotal evidence suggests that for boys who are unable to ejaculate, taking a urine sample after masturbation may help isolate some sperm.[14]

What options are available for women?

Women in a committed relationship

After chemotherapy the ovary is at risk of permanent gonadal failure,[4] and sensitivity to chemotherapy increases with age. Exposing the ovary to gonadotoxic agents accelerates the age related decline in oocyte number. Women treated with chemotherapy may have premature ovarian failure and may experience the systemic effects of oestrogen deficiency; including osteoporosis, and the psychological impact of a premature menopause, according to the agents used and the duration of treatment.

If sufficient time exists before the woman starts chemotherapy or radiotherapy, she could undergo in vitro fertilisation (IVF) to cryopreserve embryos, providing she has a normal platelet count and can

tolerate the anaesthesia needed for oocyte retrieval. As with any IVF cycle, too few oocytes may be collected or the cycle may have to be cancelled because of the risk of hyperstimulation syndrome. This is always distressing, but if this is the woman's only chance of preserving her fertility, it is devastating. Any resulting embryos will be cryopreserved and when required single embryos can be thawed and replaced in the uterus. However, only about 15% of thawed embryos result in a live birth.[15]

Is IVF safe in women with oestrogen receptor positive breast cancer?

In women with oestrogen receptor positive breast cancer, the raised oestrogen concentrations generated by IVF could accelerate the disease process,[4] although this has yet to be confirmed by prospective studies.[16] Performing ovarian stimulation with concurrent administration of an aromatase inhibitor or tamoxifen may temper this effect. This approach was used in a study of more than 100 patients who were prospectively compared with patients not undergoing fertility preservation. It did not interfere with the IVF cycle and recurrence was not increased.[17,18] A technique that avoids ovarian stimulation—whereby immature oocytes are collected and matured by in vitro maturation—has been used successfully in some women with polycystic ovary syndrome.[19] This technique might be useful in women with oestrogen receptor positive breast cancer.

After diagnosis women are generally advised not to try to conceive for up to five years[4] because they are taking adjuvant hormonal therapy, although observational evidence derived from large cohorts suggests that conceiving within two years of treatment does not influence survival.[20,21]

Several retrospective studies and one recent randomised controlled trial of 80 patients showed that suppressing ovarian activity—with a gonadotrophin hormone releasing agonist, for up to six months concurrent with chemotherapy helped preserve ovarian function—although the evidence was not conclusive.[3,22-24]

ONGOING RESEARCH

Studies are currently investigating the benefit of concurrent treatment with gonadotrophin releasing hormone analogues at the time of chemotherapy

Techniques of ovarian stimulation that avoid raising oestradiol concentrations in women with breast cancer are being refined

Surveillance of children born after the technique of in vitro maturation is ongoing

Refinements to the cryopreservation process aimed at increasing the viability of frozen oocytes are under way

Women will increasingly be having ovarian tissue reimplanted, and the reporting of outcomes should be encouraged

Retrieval of tissue from the immature testicle for subsequent reimplantation has been successful in animals and may be developed for future use in boys

A PATIENT'S PERSPECTIVE

In April 2008, at the age of 32, I was diagnosed with grade 2 invasive ductal carcinoma (oestrogen receptor positive, progesterone receptor positive, and cerbB2 positive). My recommended treatment plan was surgery followed by docetaxel, carboplatin, trastuzumab, adjuvant endocrine therapy, and local radiotherapy. I was warned that the risk of premature ovarian failure was up to 20% and I was referred to Fertility Specialists of Western Australia.

I was due to be married in 2009 and planned to start a family later that year. After counselling, and with my oncologist's consent to postpone the start of chemotherapy, I underwent a cycle of in vitro fertilisation (IVF). Because I had only a few antral follicles on vaginal ultrasound I was not suitable for the technique of in vitro maturation. I was given 112.5 IU of recombinant follicle stimulating hormone together with leuprolide acetate. Oocyte maturity was triggered with recombinant human chorionic gonadotrophin, and the eggs were retrieved on day 12 of the IVF cycle. Thirteen oocytes were retrieved and subsequently inseminated. Seven embryos were frozen for use after completion of the cancer treatment. The next week I started chemotherapy in conjunction with a gonadotrophin releasing hormone analogue.

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What options are available for single women?

Freezing oocytes

Single women, or women not in a stable relationship, cannot usually cryopreserve embryos because they must be sure that a partner would give permission for their future use. Such women can start an IVF cycle and freeze any oocytes collected, without having them fertilised. However, systematic reviews show that, despite advances in freezing techniques, for each oocyte retrieved the chance of a live birth is only 3-5%.[25,26] Expert consensus is that this technique is developmental and should not be considered routine; consequently, it is not funded by the NHS.[3,4]

Alternative strategies for single women, women with insufficient time for embryo cryopreservation, or women who are unable to countenance the further emotional or financial burden of IVF at this difficult time include freezing ovarian tissue or adopting a "wait and see" policy and relying on receiving donated oocytes if unable to conceive in the future.

Oocyte donation

Oocyte donation is a well established form of assisted reproduction—20% of embryos replaced result in a live birth (data derived from national registries).[15] Small observational studies show that both parents bond as well with their child as those couples who conceive spontaneously.[27]

Harvesting and freezing ovarian tissue

The process of harvesting ovarian tissue is less well established and still at the developmental stage.[4] Ovarian cortex is removed during laparoscopy and cryopreserved for potential reimplantation at a later date. Storage of such tissue in the UK is subject to tissue banking regulations (www.hta.gov.uk), and its availability is therefore very restricted, whereas sperm, eggs, and embryos are stored and used in a licensed centre

(Human Fertilisation and Embryology Authority; www.hfea.gov.uk). Because ovarian tissue is harvested by a surgical procedure the patient must be fit for theatre and understand the recognised potential risks.[28 29] The process of tissue removal and subsequent rapid freezing leads to cortical ischaemia, and in a study of eight women, harvested samples had lost a considerable number of follicles.[30] Few women have had the thawed ovarian tissue reimplanted, and to date this has resulted in only two live births.[31 32] Furthermore, malignant cells could theoretically be seeded; this is a particular concern in women with haematological malignancies.[33]

What are the effects of pelvic irradiation for women?

Uterine effects

Pelvic irradiation may lead to myometrial fibrosis and poor endometrial development. Small observational studies indicate an increased risk of miscarriage, growth restriction, and premature delivery depending upon the site, dose, and duration of treatment.[34 35] In one study of 33 infants born to women after abdominal irradiation, 10 weighed less than 2500 g and three died during the perinatal period.[35] Furthermore, the prepubertal uterus is thought to be more vulnerable to radiotherapy than the mature one, so radiotherapy might cause irreparable impairment of uterine growth.[34 36 37]

Ovarian failure

Patients undergoing pelvic irradiation should be warned of the gonadotoxic effect of radiation, which accelerates the natural process of ovarian ageing.[3 4] Radiotherapists can predict the likelihood of ovarian failure by using a modified model of natural oocyte decline.[38] Performing laparoscopic ovarian transposition—by moving the ovary on its vascular pedicle laterally from the incident radiation—can minimise exposure to ionising radiation and reduces incident pelvic radiation, according to the site of treatment and the distance the ovary is moved.[39] Subsequent spontaneous conception may occur, but if IVF is needed the ovaries may require repositioning to enable vaginal access, or the patient may need to undergo laparoscopic egg collection.

Additional educational resources

Resources for healthcare professionals

Royal College of Physicians, Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists Working Party. *The effects of cancer treatment on reproductive functions. Guidance on management*. www.rcog.org.uk/resources/public/pdf/EffectCancerRepro.pdf

American Society of Clinical Oncology. *Recommendations on fertility preservation in cancer patients*.http://jco.ascopubs.org/cgi/content/full/24/18/2917

National Institute for Health and Clinical Excellence. *Fertility: assessment and treatment for people with fertility problems*. 2004. www.nice.org.uk/guidance/index.jsp?action=byID&r=true&o=10936

Human Fertilisation and Embryology Authority (www.hfea.gov.uk)—The UK's independent regulator overseeing the use of gametes and embryos in fertility treatment and research

Resources for patients

American Society for Reproductive Medicine. *Patient's fact sheet for fertility preservation*. 2004. www.asrm.org/Patients/FactSheets/cancer.pdf

SUMMARY POINTS

Warn patients of the possible effects that treatment may have on their reproductive capacity

Provide access to a fertility specialist and supportive counselling

Sperm banking is an effective and well established technique for adolescent boys and men

Women should be offered access to oocyte or embryo freezing if sufficient time is available before treatment begins

Oocyte cryostorage has limited success and freezing of ovarian tissue is still experimental

What are the effects of cranial irradiation?

Cranial irradiation may initiate hypogonadotrophic hypogonadism. If this occurs, ovulation or spermatogenesis will need to be induced with both exogenous follicle stimulating hormone and luteinising hormone or human chorionic gonadotrophin.

What options are available for children and adolescents?

Children pose a difficult ethical problem because although they may have some insight into the potential effect of their cancer treatment on their fertility, it is usually their parents who are more worried about preserving reproductive function.

The prepubertal testicle is more vulnerable to the cytotoxic effects of chemotherapy than the adult testicle.[7] As described, adolescent boys may be able to store a semen sample, but those who cannot produce one by masturbation may find that penile vibratory stimulation is more successful. Ethical board approval may be needed before considering surgery for testicular extraction of sperm in an adolescent boy. The retrieval of precursors of spermatozoa or spermatogonial stem cells for subsequent reimplantation or in vitro maturation for use in IVF has not been used in prepubertal boys, although it has been successful in animal models.[7] The production of testosterone by Leydig cells can be preserved after chemotherapy, and in such cases normal pubertal progression would be expected.[7]

The prepubertal and early adolescent ovary is less vulnerable to the effects of chemotherapy and radiotherapy than the mature ovary. None the less, after counselling, girls undergoing radiotherapy or chemotherapy may be considered for ovarian tissue harvesting—a hospital ethics committee should help with such decisions.[40]

How should a doctor discuss these effects with a patient?

Observational studies indicate that, despite most patients' desire to be informed about the effects of

cancer treatment on their fertility,[3] many doctors and family members tend to focus on the immediate treatment of a patient with a life threatening illness,[6] and only a minority of patients receive this advice.[41 42]

The implications of a patient's treatment on their fertility will depend on the patient's age, understanding, the type of cancer, and treatment. Any doctor-patient discussion will be influenced by the wishes of a partner if the patient is in a relationship. The chance of a live birth is substantially better for a woman who freezes embryos than for one who freezes unfertilised eggs. A woman may have to make a difficult decision about the strength of a current relationship as she tries to decide whether to freeze embryos or eggs, set against a background state of distress due to a recent diagnosis of cancer, the threat of chemotherapy and possible menopause. Supportive counselling by a trained fertility counsellor is therefore essential.[3 4]

In the UK, IVF treatment cannot be offered to a couple unless it is in the best interests of the child born from the treatment. Consequently the treating IVF clinician and counselling staff should take a broad view before starting treatment.

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Provenance and peer review: This review was encouraged but not commissioned; it was externally peer reviewed.

Patient consent obtained.

1 Office of Cancer Survivorship. *Facts about cancer survivorship*. Bethesda: National Cancer Institute, 2005.
2 Cancer Research UK. *CancerStats key facts all cancers*. 2008. http://info.cancerresearchuk.org/cancerstats/incidence/.
3 Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917-31.
4 Royal College of Physicians, Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists. *The effects of cancer treatment on reproductive functions. Guidance on management. Report of a working party*. 2007. www.rcog.org.uk/resources/public/pdf/EffectCancerRepro.pdf.
5 National Institute for Health and Clinical Excellence. *Fertility assessment and treatment for people with fertility problems.* 2004. www.rcog.org.uk/resources/Public/pdf/Fertility_summary.pdf.
6 Quinn GP, Vadaparampil ST, Bell-Ellison BA, Gwede CK, Albrecht TL. Patient-physician communication barriers regarding fertility preservation among newly diagnosed cancer patients. *Soc Sci Med* 2008;66:784-9.
7 Revel A, Revel-Vilk S. Pediatric fertility preservation: is it time to offer testicular tissue cryopreservation? *Mol Cell Endocrinol* 2008;282:143-9.
8 Sanger WG, Olson JH, Sherman JK. Semen cryobanking for men with cancer—criteria change. *Fertil Steril* 1992;58:1024-7.
9 Lass A, Akagbosu F, Brinsden P. Sperm banking and assisted reproduction treatment for couples following cancer treatment of the male partner. *Hum Reprod Update* 2001;7:370-7.
10 Kelleher S, Wishart SM, Liu PY, Turner L, Di Pierro I, Conway AJ, et al. Long-term outcomes of elective human sperm cryostorage. *Hum Reprod* 2001;16:2632-9.
11 Hoy J, Venn A, Halliday J, Kovacs G, Waalwyk K. Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria, Australia. *Hum Reprod* 1999;14:1760-4.
12 Lansac J, Royere D. Follow-up studies of children born after frozen sperm donation. *Hum Reprod Update* 2001;7:33-7.
13 O'Flaherty C, Vaisheva F, Hales BF, Chan P, Robaire B. Characterization of sperm chromatin quality in testicular cancer and Hodgkin's lymphoma patients prior to chemotherapy. *Hum Reprod* 2008;23:1044-52.
14 Bahadur G, Ling KL, Hart R, Ralph D, Riley V, Wafa R, et al. Semen production in adolescent cancer patients. *Hum Reprod* 2002;17:2654-6.
15 Wang YA Dean JH, Sullivan EA. Assisted reproduction technology in Australia and New Zealand 2005. In: Unit ANPS, ed. *Assisted reproduction technology series no. 11*. Sydney: Australian Institute of Health and Welfare, 2007.
16 Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. *J Clin Endocrinol Metab* 2006;91:3885-90.
17 Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2005;23:4347-53.
18 Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol* 2008;26:2630-5.
19 Reinblatt SL, Buckett W. In vitro maturation for patients with polycystic ovary syndrome. *Semin Reprod Med* 2008;26:121-6.
20 Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast* 2007;16(suppl 2):S175-81.
21 Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. *BMJ* 2007;334:194.
22 Oktay K, Sonmezer M, Oktem O, Fox K, Emons G, Bang H. Absence of conclusive evidence for the safety and efficacy of gonadotropin-releasing hormone analogue treatment in protecting against chemotherapy-induced gonadal injury. *Oncologist* 2007;12:1055-66.
23 Blumenfeld Z, Avivi I, Eckman A, Epelbaum R, Rowe JM, Dann EJ. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. *Fertil Steril* 2008;89:166-73.
24 Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. *Fertil Steril* 2008 Aug 1 Epub ahead of print.
25 Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. *Fertil Steril* 2006;86:70-80.
26 Gook DA, Edgar DH. Human oocyte cryopreservation. *Hum Reprod Update* 2007;13:591-605.
27 Golombok S, Jadva V, Lycett E, Murray C, Maccallum F. Families created by gamete donation: follow-up at age 2. *Hum Reprod* 2005;20:286-93.
28 Hart R, Ruach M, Magos A. Is laparoscopic surgery really worth it? The views of patients, hospital doctors and health care managers. *Gynaecol Endosc* 2001;10:289-96.
29 Ahmad G, Duffy JM, Phillips K, Watson A. Laparoscopic entry techniques. *Cochrane Database Syst Rev* 2008;(2):CD006583.
30 Newton H, Aubard Y, Rutherford A, Sharma V, Gosden R. Low temperature storage and grafting of human ovarian tissue. *Hum Reprod* 1996;11:1487-91.
31 Demeestere I, Simon P, Emiliani S, Delbaere A, Englert Y. Fertility preservation: successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease. *Oncologist* 2007;12:1437-42.
32 Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* 2004;364:1405-10.
33 Meirow D, Hardan I, Dor J, Fridman E, Elizur S, Ra'anani H, et al. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. *Hum Reprod* 2008;23:1007-13.
34 Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr* 2005;34:64-8.
35 Green DM, Fine WE, Li FP. Offspring of patients treated for unilateral Wilms' tumor in childhood. *Cancer* 1982;49:2285-8.
36 Holm K, Nysom K, Brocks V, Hertz H, Jacobsen N, Muller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. *Bone Marrow Transplant* 1999;23:259-63.
37 Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004;83:96-102.
38 Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005;62:738-44.
39 Hart R, Sawyer E, Magos A. Case report of ovarian transposition and review of literature. *Gynaecol Endosc* 1999;8:51-4.
40 Deepinder F, Agarwal A. Technical and ethical challenges of fertility preservation in young cancer patients. *Reprod Biomed Online* 2008;16:784-91.
41 Zebrack BJ, Casillas J, Nohr L, Adams H, Zeltzer LK. Fertility issues for young adult survivors of childhood cancer. *Psychooncology* 2004;13:689-99.
42 Duffy CM, Allen SM, Clark MA. Discussions regarding reproductive health for young women with breast cancer undergoing chemotherapy. *J Clin Oncol* 2005;23:766-73.