While ovarian tissue cryopreservation has commonly been equated with fertility preservation in cancer patients, there is a range of alternative options to preserve fertility. Based on the type and timing of chemotherapy, the type of cancer, the patient’s age and the partner status, a different strategy of fertility preservation may be needed. If the patient has a partner or accepts donor sperm, embryo cryopreservation should be considered first, since this is a clinically well established procedure. Despite relatively low pregnancy rates, when there is time for ovarian stimulation and the patient is single, oocyte cryopreservation may also be preferred to ovarian tissue banking. In breast cancer patients, tamoxifen or aromatase inhibitors can be used for ovarian stimulation prior to oocyte or embryo cryopreservation. In endometrial cancer patients, aromatase inhibitors may be the only choice for ovarian stimulation. When only pelvic radiotherapy is used, ovarian transposition can be performed, but the success rates vary because of scatter radiation and vascular compromise. Lack of FSH and GnRH receptors on primordial follicles and oocytes does not make gonadal suppression an effective strategy of gonadal protection. Fertility preservation should be an integral part of improving the quality of life in cancer survivors; however, it is neither possible nor ethical to recommend the same recipe for every cancer patient.

Key words: cancer/cryopreservation/fertility preservation/ovarian transplantation/ovulation induction

Introduction

In recent issues of Human Reproduction, several articles have debated whether ovarian cryopreservation, and subsequent transplantation should be offered to cancer patients (Kim, 2003; Revel and Schenker, 2003). Every year, hundreds of thousands of women and children are exposed to potentially sterilizing chemotherapy and radical surgery for the treatment of cancer as well as for benign conditions (Oktay and Yih, 2002; Jemal et al., 2003). Because of the variations in type and dose of chemotherapy, the type of cancer, the time available prior to onset of treatment, the patient’s age and the partner status, each case is unique and requires a different strategy of fertility preservation. For example, a 12-year-old child who is undergoing stem cell transplantation is extremely likely to suffer from premature ovarian failure as a result of the heavy chemotherapy and/or radiotherapy that she will receive (Teinturier et al., 1998; Couto-Silva et al., 2001). For this patient, there is no other option but the experimental ovarian cryopreservation to preserve her fertility. Many adult cancer patients are started on chemotherapy within days of diagnosis, and they do not have sufficient time to undergo an ovarian stimulation for the purpose of embryo or oocyte cryopreservation. For these patients too, ovarian cryopreservation is the only experimental option.

What about single patients? Assuming that they have sufficient time to undergo ovarian stimulation, they can either use donor sperm and cryopreserve embryos, which is not acceptable for all, or resort to another experimental procedure, oocyte cryopreservation. Even though there have been recent reports of improved success (Fabbri et al., 1998), an analysis of the peer-reviewed literature indicates only a 3–4% pregnancy rate per thawed oocyte (Oktay et al., 2001a). Since there have been pregnancies with this procedure, oocyte cryopreservation stands one notch above ovarian tissue cryopreservation but still below embryo cryopreservation. When there is time for fully fledged ovarian stimulation, and the centre is experienced in cryopreservation of oocytes, this approach should be considered first. In some cases where a large number of oocytes could not be obtained, ovarian cryopreservation can follow oocyte cryopreservation in the same patient.

One exception to not having sufficient time between diagnosis of cancer and chemotherapy is breast cancer. Typically a 6-week period is allowed between surgery and...
chemotherapy in breast cancer patients, but standard ovarian stimulation is not considered safe in these patients. In these patients, tamoxifen can be used, alone or in combination with FSH, for ovarian stimulation and embryo and/or oocyte cryopreservation (Oktay et al., 2003a,b). With use of tamoxifen alone or in combination with FSH, embryo yield ranged from zero to six per patient and, with up to 3 years of follow-up, none of the patients (stage I–III) had cancer recurrence. Most of these patients will not be allowed to conceive for several years either because they will be receiving tamoxifen for 5 years or because of the fear of cancer recurrence. Thus, pregnancy outcome data are not likely to be available for a number of years. Another possibility for ovarian stimulation in patients with estrogen-dependent cancer is the use of aromatase inhibitors, which are emerging as alternatives to tamoxifen in the treatment of breast cancer (Smith and Dowsett, 2003). Aromatase inhibitors have been used successfully in infertility patients for ovulation induction (Mitwally and Casper, 2003) but its use in breast cancer patients is currently under investigation (Oktay, in press; Sonmez and Oktay, 2004). Ovulation induction with aromatase inhibitors may also be used to preserve fertility via embryo cryopreservation in endometrial cancer patients prior to radical surgery (Oktay et al., 2003c). Because tamoxifen has an agonistic effect on the endometrium, it cannot be used in patients with endometrial cancer.

The risk of reseeding cancer by ovarian transplantation should be neither ignored nor exaggerated. Because clinical experience with ovarian transplantation currently is limited (Oktay and Karlakaya, 2000; Oktay et al., 2001b; Radford et al., 2001), it is not yet known whether the actual risk of cancer recurrence is increased in these patients. Most cancers in women of reproductive age do not metastasize to ovaries (Oktay, 2001).

Kim argued that breast cancer is a contraindication for ovarian cryopreservation and transplantation (Kim, 2003). Breast cancer metastasizes haematogenously. Previous studies indicated that in the absence of systemic metastasis (stage I–III), and if the pelvic exam and ultrasound are normal, occult ovarian involvement is rare in breast cancer (Curtin et al., 1994). Even then, most of the occult metastases belong to the less common histological type, the infiltrating lobular (15% of all breast cancer) as opposed to the invasive ductal cancer which constitute >70% of all breast cancers (Young and Scully, 1987; Morrow, 2001; Perrotin et al., 2001; Li et al., 2003). Moreover, lobular cancer typically occurs in post-reproductive age women (Sastre-Garau et al., 1996; Li et al., 2003), and ovarian metastasis occurs more commonly in advanced stage cancer (Gagnon and Tetu, 1989; Hann et al., 2000). Our shared experience with the Memorial Sloan Kettering Cancer Center corroborates these findings, and indicates that diagnosis of stage I–III breast cancer of invasive ductal type is not a contraindication for ovarian cryopreservation or transplantation. Nevertheless, prior to cryopreservation or transplantation, we require a thorough evaluation of the patient and the tissue to rule out ovarian metastasis, in all cases. It should also be born in mind that some of the young breast cancer patients may have BRCA gene mutations and, as a result, may harbour a co-existing primary ovarian cancer (Liede and Narod, 2002). Even though ovarian cancer is rare prior to the age of 35 years (Massi et al., 1996), these patients should be counselled about that risk.

When there is ovarian involvement, or when potential for occult metastasis is high, however, ovarian tissue should not be cryopreserved for the purpose of autotransplantation. In theory, normal appearing ovarian tissue can be cryopreserved with the idea of future in vitro maturation of primordial follicles and xenografting (Oktay et al., 1998, 2000; Weissman et al., 1999; Revel et al., 2000; Smitz and Cortvriendt, 2002; O’Brien et al., 2003). Since neither of these technologies is clinically possible yet, in vitro maturation and xenografting represent the most experimental end of the spectrum of fertility preservation.

One of the major limiting factors in success of ovarian transplantation of ovarian cortical strips is the large loss of primordial follicles due to initial ischaemia (Baird et al., 1999). The loss attributable to the cryopreservation procedure is relatively smaller (Aubard et al., 1999; Liu et al., 2002). Reports on orthotopic and heterotopic ovarian transplantation with cryopreserved tissue suggested ovarian function for up to 9 months (Oktay and Karlakaya, 2000; Callejo et al., 2001; Radford et al., 2001). However, in all the cases reported, either the patients were exposed to prior chemotherapy or ovarian surgery, or they were perimenopausal. Thus, it is difficult to determine the full potential of this procedure based on the reported cases. On the other hand, the two relatively younger patients who underwent heterotopic ovarian transplantation with fresh tissue had nearly 3 years of ovarian function (Oktay et al., 2003d). Nevertheless, because of the potential limited life span of ovarian transplants, the procedure should only be carried out for fertility restoration, and when the patient is ready to conceive. In theory, even a year’s time may be sufficient to obtain oocytes for IVF and embryo transfer. Clinical studies are in progress to test the potential of heterotopic ovarian transplants to restore fertility. In the meantime, the first pregnancy after heterotopic ovarian transplantation in non-human primates has already been reported (Lee et al., 2003).

Revel and Schenker (2003) eloquently described the controversy surrounding the use of GnRH analogues for fertility preservation. There is no question that a large randomized study is needed to put this controversy to rest. We do not recommend these drugs as an effective way of fertility preservation. Approximately 90% of all ovarian follicles are at the resting stage and they do not express FSH receptors (Lass et al., 1997; Oktay et al., 1997), nor do these follicles require FSH to initiate growth (Oktay et al., 1998; McNatty et al., 1999; Meduri et al., 2003). Since the main aim of preserving fertility in these patients is to preserve ovarian reserve made up of primordial follicles, the rationale for pituitary/gonadal suppression is unclear. It has been speculated that this could be a direct effect modulated through GnRH receptors (Blumenfeld, 2003). Even though there has been some evidence that these receptors may be present on luteinized immortalized granulose cell lines (Cheng et al., 2002), to our knowledge, no study showed the presence of these receptors on human primordial follicles or oocytes. In
evaluating findings from animal studies, significant interspecies differences in ovarian physiology should also be taken into account. A clinical example of why gonadal suppression may not protect ovaries is the fact that prepubertal children who undergo heavy chemotherapy still suffer from ovarian failure (Teinturier et al., 1998). However, since younger patients have a larger ovarian reserve, the fact that immediate ovarian failure did not occur does not mean that the gonads were unaffected by the chemotherapy. All of the patients who receive heavy gonadotoxic chemotherapy will suffer from premature ovarian failure (Grigg et al., 2000).

Even though it is not within the scope of this debate, ovarian transposition procedure deserves a mention. Ovarian transposition can only be used when pelvic radiotherapy is used alone. This procedure has a variable success rate, however, ranging from 16 to 90% due to scatter radiation and vascular compromise, and depending on the age of the patient, dose of radiation, and whether intracavitary brachytherapy or pelvic external beam irradiation is used (Hunter et al., 1980; Anderson et al., 1993; Clough et al., 1996; Morice et al., 2000; Meirow and Nugent, 2001). In addition, should these patients need IVF in the future, oocyte retrieval may become technically more challenging.

**Conclusions**

The approach to fertility preservation should be individualized. In our centre, we have developed the following comprehensive approach (Figure 1) which encompasses nearly all experimental strategies. Just like ovarian cryopreservation, oocyte and embryo cryopreservation for cancer patients should only be studied under Institutional Review Board/Ethics Committee-approved protocols. It is neither possible nor ethical to recommend the same recipe for every cancer patient. Physicians who are dealing with fertility preservation should familiarize themselves with medical oncology, histopathology and reproductive endocrinology. In every case, reproductive endocrinologists should work hand in hand with the patients’ medical doctor.

Whether or not ovarian cryopreservation and transplantation will make an impact on public health is unclear. What is clear is that fertility preservation should be an integral part of improving the quality of life in cancer survivors.

**References**


Clough KB, Goffine F, Labib A, Renolleau C, Campana F, de la Rocheforidiere


Oktay K. Fertility preservation in female cancer patients. CME J Gynecol Oncol. In press.