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REVIEW ARTICLE

Cancer and fertility preservation: Barcelona consensus meeting*

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Abstract

Improvements in early diagnosis and treatment strategies in cancer patients have enabled younger women with cancer to survive. In addition to the stressful event of the diagnosis, patients with malignant diseases face the potential loss of the opportunity to have children. Preservation of fertility has become a challenging issue and it is still surrounded by controversies. On the basis of available evidence, a group of experts reached a consensus regarding the options for trying to preserve fertility in women with cancer: among established methods, in postpubertal women, oocyte cryopreservation is the preferred option, whereas ovarian tissue cryopreservation is the only possibility for prepubertal girls. Combining several strategies on an individual basis may improve the chances of success. Realistic information should be provided before any intervention is initiated. Counseling should offer support for patients and provide better care by understanding emotional needs, psychological predictors of distress and methods of coping. Early referral to the fertility specialist is essential as fertility preservation (FP) may improve quality of life in these patients. The information summarized here is intended to help specialists involved in the treatment of cancer and reproductive medicine to improve their understanding of procedures available for FP in young cancer patients.

Keywords

Cancer, consensus, fertility preservation, oocyte vitrification, ovarian tissue cryopreservation

History

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Introduction

Advances in the diagnosis and treatment of cancer have resulted in increased life expectancy of oncological patients. Long-term cancer survivors, however, are faced with different effects of treatment, including the risk of infertility. In a recent survey, it was found that 61% of women who received treatment that potentially could affect fertility were counseled by the oncology team [1]. One of the reasons given by doctors is lack of knowledge about reproductive options.

Methods

This updated review addresses controversial issues related to the best approach and treatment options for cancer in female patients who are concerned of preserving and managing their fertility (Table 1). Conclusions reached by a group of experts on the panel of the ''Fertility Preservation Update: Consensus Meeting'', which was held in Barcelona, Spain, in June 6–7, 2011, and organized by Dexeus Foundation, Woman's Health and BIOCAT International Centre for Scientific Debate are here reported, with the literature updating during the preparation of this manuscript.

Results

Epidemiology of cancer in childhood and young adults

Cancer in childhood is uncommon (only accounts for 1% of all diagnosed malignancies) but is the second cause of mortality in this stage of life, only surpassed by unintended injuries. Each year between 12 000 and 15 000 children and adolescents younger than 20 years are diagnosed with cancer in the US [2]. Owing to improvements in diagnosis and treatment, survival has improved dramatically, with current survival rates nearing 75% for children and adolescents. Estimates suggest that by 2010, one in 715 people in the UK survived cancer during childhood [3].

Prevention in childhood cancer is not useful and there is a high risk of sequelae in the developing tissues secondary to the intensity and modalities of cancer therapy. The younger the patient, the most susceptible is to the effect of treatment. Also, the more aggressive the treatment, the most increase is in survival. Increasing survival trends over time have been consistently demonstrated in children and adolescents/young adults over the past 40 years [4,5], with five-year survival rates now approaching 80% [6].

With this increase in rates of survivorship has come the recognition that survivors are at risk for adverse health and

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Table 1. The gap between current and recommended best practice and the learning objectives of this review.

Best practice	Current practice	Resulting gaps	Learning objectives
Counseling on FP to all cancer patients	<50% oncologist referred patients to a reproductive specialist	To sensitize and provide information on FP to oncologists and physicians who treat cancer patients	To know the mechanisms by which oncological treatments affect fertility. To know current techniques and possibilities of FP
Cryopreservation of oocytes for FP in the adult woman	Cryopreservation of embryos	Results of freezing of embryos, oocytes and oocyte vitrification. Separation rates up to 50% of couples after cancer have been reported	Current results of oocyte vitrification are superior to slow freezing, without the potential conflicts generated by cryopreserved embryos
Obtaining mature oocytes without delay of cancer treatment	Stimulation treatment 2–4 weeks. Waiting until next menses to start stimulation or doing ovarian tissue freezing when not enough time	Possibility of immediate treatment. Some women may be denied FP strategies in order to avoid a delay in the oncologic treatment	Early luteolysis and immediate stimulation, protocols for hormone-dependent cancer
Cryopreservation of ovarian tissue perspectives of vitrification	Slow freezing of ovarian tissue	Improvements of freezing techniques	Potential of vitrification of ovarian tissue
Combined FP techniques	Each center the technique to which is more familiarized	Multidisciplinary teams with experience and facilities	

quality-of-life outcomes, including decreased fertility, overall reduction in quality of life and early death [6,7]. In a prospective assessment of the prevalence of gonadal insufficiency in a cohort of 126 Spanish pediatric cancer survivors [8], 8% of boys had delayed puberty and 19% of girls had advanced/precocious puberty. In girls, signs of partial ovarian insufficiency (elevated FSH and/or LH) were found in 16.7% of cases. Risk factors included gonadal radiotherapy and highly gonadotoxic chemotherapy.

The most commonly occurring cancers among young people aged 15–24 years in Europe include Hodgkin's lymphoma, testicular cancer and malignant melanoma [9,10]. The cancers most frequently diagnosed in adults aged 25–49 years include breast, colorectal and cervical cancer and malignant melanoma [9].

Therefore, at the time of assessing the effect of cancer on fertility and planning for fertility preservation (FP), it is important to consider that the critical period ranges between puberty and premenopausal age, preferably before 35 years in women.

Table 2. Risks of permanent amenorrhea in women treated with modern chemotherapy and radiotherapy (adapted from Lee et al. [13]).

High risk (80%)	BMT with Cy/TBI or Cy/busulfan radiation to a field that includes the ovaries
	CMF, CEF, CAF ×6 in women >40 years
Intermediate risk	CMF, CEF, CAF ×6 in women age 30–39 years
	AC ×4 in women age >40 years
Lower risk (20%)	ABVD, CHOP ×4–6
	AML therapy (anthracycline/cytarabine)
	ALL therapy (multi-agent)
	CMF, CEF, CAF ×6 in women <30 years
	AC ×4 in women <40 years

BMT, bone marrow transplantation; Cy, cyclophosphamide; TBI, total body irradiation; CMF, cyclophosphamide, methotrexate and fluorouracil; CEF, cyclophosphamide, epirubicin and fluorouracil; CAF, cyclophosphamide, doxorubicin and fluorouracil; AC, doxorubicin and cyclophosphamide; ABVD, doxorubicin/bleomycin/vinblastin/dacarbazine; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone.

Effects of chemotherapy and radiotherapy on fertility

It is important to evaluate the risks of different chemotherapy and radiotherapy treatments on fertility and the role of age before planning for FP [11]. The risk of permanent premature ovarian failure is considered high when the probability of permanent amenorrhea is $\geq$80%, intermediate when <80% and >20% and low when $\leq$20% [12] (Table 2).

At birth, the ovary contains a finite number of oocytes that are surrounded by a single layer of pregranulosa cells to form primordial follicles. Ovarian reserve (OR) refers to the current number of follicles/oocytes a woman has in her ovaries [13]. Through the life cycle, there is an ongoing decline in the number of primordial follicles and in a recent study of human OR from conception to menopause, it is shown that 95% of the fluctuation in follicular reserve is owing to age alone for ages up to 25 years [14].

Anticancer drugs may diminish the primordial follicle pool, cause ovarian atrophy and harm the ovarian blood vasculature. The exact mechanism of toxicity of chemotherapy on female reproduction still remains unclear. The follicular target of chemotherapy could be the granulosa cells of primordial follicles and damage to these supporting cells leads to destruction of the follicle, as shown by a decline of anti-Müllerian hormone (AMH) and inhibin B levels in response to chemotherapy [15]. It is possible that repeated acute drops in AMH would accelerate or enhance recruitment and maturation of a new cohort of primordial follicles, which subsequently would become vulnerable to ensuing series of chemotherapy resulting eventually in a ''burn-out'' of the primordial follicle reserve [15].

The extent of damage is related to the patient's age, chemotherapeutic agent and drug regimen used. Different chemotherapeutic agents have differential effects on OR, with alkylating agents inducing the greatest damage [16]. On the other hand, patients who undergo bone marrow transplantation have extremely high ovarian failure rates, ranging from 72% to 100% [17]. In a large cohort of subjects enrolled in the Childhood Cancer Survivor Study, the risk of acute ovarian failure varied according to the type of tumor, with an odds ratio of 3.8 for Hodgkin's disease, 3.2 for non-Hodgkin's lymphoma, 3.0 for Wilm's tumor, 2.6 for sarcoma and 1.0 for leukemia [18].

Pretreatment clinical parameters, such as the presence of menses, regular cycles or previous pregnancy do not accurately reflect the status of OR. In a study of 138 premenopausal women with loco-regional breast cancer, age at the time of diagnosis and systemic chemotherapy were the strongest predictors of menopause one year later [19]. Plasma levels of FSH and estradiol in the early follicular phase have a low-moderate predictive value [20]. AMH levels are a better indicator of progressive decrease of follicles/oocytes pool with age [21] and may have a predictive value of the OR status after chemotherapy [15]. In a study of 37 women previously treated with gonadotoxic agents for hematological malignancies, serum AMH concentrations were measured in order to assess the OR. Although in most patients treated with chemotherapy, menstrual cyclicity was restored, median serum AMH levels were lower than in controls [22]. In a cross-sectional evaluation of markers of OR in women exposed to cytotoxic chemotherapy for early stage breast cancer and matched controls, the same significant differences were observed between the two groups in antral follicle count and AMH [23]. Moreover, a recent study indicated that AMH can be used as a direct marker of OR to predict long-term ovarian activity after chemotherapy, although these findings are limited by the sample size [24]. Age remains an important factor in the recovery of endocrine function, and return of menses is a surrogate sign. The interpretation of very low AMH values in terms of fertility remains unclear as pregnancies have been recorded after ovarian tissue transplantation with undetectable AMH [25]. Further research is needed to determine the impact of cancer treatments on markers of OR and any correlation with future fertility, and counseling on likelihood of natural or assisted conception should be done with caution.

Chemotherapeutic agents may cause DNA damage and chromosomal anomalies in oocytes leading to an increased risk of abortions or congenital malformations. The safety of using IVF and embryo cryopreservation in cancer patients who have recently undergone chemotherapy treatments is still questionable; therefore, oocyte retrieval for IVF after recent exposure to chemotherapy (up to six months) should be avoided [26].

Radiotherapy to the pelvis results in ovarian injury and diminished follicle reserve; the extent of damage is largely based on patient's age, treatment dose and irradiation field. Abdominal radiation at doses of 20–30 Gy results in ovarian failure in 97% of cases and in 72% of cases after radiation exposure at prepubertal age. A single dose of 10–15 Gy of total body irradiation results in premature ovarian failure [27]. However, doses of ovarian radiation of less than 10 Gy are capable of inducing acute ovarian failure in patients who have additional risk factors, namely concomitant exposure to alkylating agents and older age at diagnosis [18]. Also, the effect of radiation on the uterus (reduction in the uterine size and endometrial thickness) may adversely affect success of IVF [28]. Exposure of the pelvis to radiation is associated with increased obstetric and neonatal risks (miscarriage, uterine rupture, placenta accrete, mid-trimester pregnancy loss, preterm birth and low birthweight) [29].

There is a need for greater international collaboration in the study of trans-generational effects of cancer treatment in children and adolescents.

Fertility preservation

The American Society of Clinical Oncology recommendations on FP in cancer patients indicate that all patients susceptible of treatment with radiotherapy and chemotherapy should be informed and counseling depends on age, disease, prognosis and interval time for freezing. The urgency to begin cancer treatment should not be an excuse to delay FP [30].

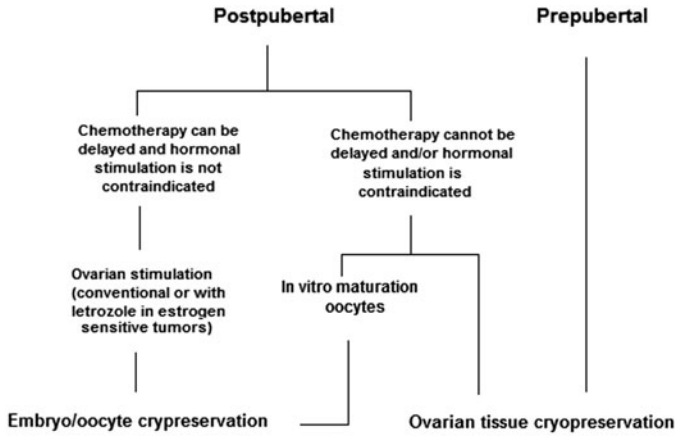

Figure 1. Suggested algorithm for female FP.

The risk of gonadal failure should be carefully analyzed and will depend on intrinsic (mainly age and health status of the patient) and extrinsic factors (nature of predicted treatment). However, it remains difficult to predict which patients will really develop a premature gonadal failure. In patients at high risk of infertility, FP should be offered, regardless of the prepubertal status as the prepubertal gonad is not protected. FP counseling should also consider issues such as time available and team expertise. Proper consent forms should be obtained in every case.

There are several strategies for FP in the female patient, and the choice will depend on the age of the patient, type of disease and treatment required, and time availability before the onset of chemotherapy. The most established methods are embryo or oocyte cryopreservation, although they require time and no contraindication for ovarian stimulation. These limiting steps can be overcome by several strategies. When high levels of estradiol should be avoided (in the case of hormone sensitive tumors), aromatase inhibitors combined with gonadotropins for ovarian stimulation can be used.

When there is no time for conventional ovarian stimulation, gonadotropin-releasing hormone (GnRH) antagonist is effective to induce luteolysis. To save time and to avoid high levels of estradiol, immediate oocyte retrieval without previous stimulation is also feasible. In this case, *in vitro* maturation (IVM) of immature oocytes is required (see ''IVM of oocytes'' section).

Ovarian tissue freezing is the only method available in prepubertal girls and will be the method of choice whenever there is no time or ovarian stimulation is not allowed. Ovarian transposition is indicated in the cases of pelvic radiotherapy and should always be combined with cortical strips freezing [30].

It has been shown that the use of GnRH agonist as a cotreatment before and during chemotherapy may protect ovarian germline stem cells [13] even though there is insufficient evidence to demonstrate its effectiveness.

Currently, there is a trend toward combining different strategies in order to maximize the changes of success. Figure 1 shows an algorithm for female FP.

Ovarian stimulation

Treatment is required for controlled ovarian stimulation to obtain mature oocytes for cryopreservation or fertilization and embryo cryopreservation. Performance of ovarian stimulation in cancer patients will mainly depend on patients' pretreatment OR, highly correlated with the patient's age [20]. In hormone-dependent tumors, high levels of estradiol should be avoided and for this reason, special protocols for optimizing controlled ovarian hyperstimulation (COH) have been designed, which allow to

obtain a larger number of oocytes with lower levels of estradiol [31,32]. It has been shown that GnRH agonist trigger instead of human chorionic gonadotropin improves outcomes by increasing the yield of mature oocytes and embryos in aromatase inhibitor cycles and also decreases the post-trigger estradiol exposure as well as the risks of ovarian hyperstimulation syndrome in women with breast cancer [33].

There is still controversy on whether cancer patients may have a diminished ovarian response to stimulation prior to antineoplastic therapy suggesting that cancer per se may impair OR [34,35]. A recent meta-analysis of seven retrospective, case-controlled studies concluded that women with malignant diseases should expect a lower number of oocytes retrieved after COH for FP, compared with healthy, age-matched patients [36].

The possibility of immediate pituitary blockade with a GnRH antagonist allows obtaining mature oocytes when ovarian stimulation is started in the luteal phase in situations in which there is no sufficient time for conventional follicular phase oocyte retrieval before chemotherapy [37].

IVM of oocytes

The technique of IVM of oocytes is a complementary strategy in FP. Retrieved oocytes either at metaphase I or at prophase I (germinal vesicle) can be cultured in IVM media and oocytes matured in culture to metaphase II can be cryopreserved for FP.

IVM of immature oocytes has been applied to improve the mature oocyte yield of breast cancer patients undergoing ovarian stimulation for FP [33,37] and after immature oocyte retrieval in the luteal phase in patients undergoing imminent gonadotoxic treatment [38,39]. A comparison of the results of IVM of oocytes for FP performed during the luteal phase of the cycle with those of IVM performed during the follicular phase in cancer patients showed no significant differences in the number of retrieved oocytes, maturation rates, fertilization rates or the total number of oocytes and embryos that were cryopreserved [39,40]. It has been shown that vitrification of IVM oocytes yields satisfactory results, with a survival rate around 65%, fertilization rate close to 65%, implantation rate of 25%, clinical pregnancy rate 10–18% and miscarriage rate ranging between 20% and 50% [41]. Although healthy live births can be achieved from the combination of IVM oocytes and vitrification, vitrification of *in vitro* matured oocytes is less effective than vitrification of in vivo matured oocytes [42].

The combination of immature oocyte collection from biopsied pieces of ovarian tissue and subsequent cryopreservation of both *in vitro* matured oocytes and ovarian tissue may result in increased chances for future fertility in certain patients. The cryopreservation of IVM oocytes alone or combined with tissue cryopreservation is a realistic option for FP when ovarian stimulation cannot be performed.

Oocyte cryopreservation: slow freezing and vitrification

Oocyte cryopreservation is currently the most common FP technique. The oocyte is particularly susceptible to damage during cryopreservation, including meiotic spindle depolymerization, zona pellucida hardening, cytoplasmic and cytoskeleton damage, polar body degeneration/fusion as well as oocyte aging.

Slow freezing has been used as the cryopreservation technique for many years [43] but recently vitrification [44] has been shown to give better results in terms of survival, pregnancy and implantation rates. Different studies have shown that cryopreservation of mature human oocytes with vitrification is more efficient at establishing a pregnancy than slow-rate freezing [45].

The clinical pregnancy rate has doubled with the introduction of oocyte vitrification in ''open'' systems (into direct contact with liquid nitrogen) [46]. On the other hand, efficiency in donation programs is not compromised with oocyte vitrification [47,48]. The laboratory efficiency of the technique has also been demonstrated in a prospective randomized study with own sibling oocytes [49]. Cumulative ongoing pregnancy rates with oocyte vitrification without embryo selection in a standard infertility program are comparable to what obtained with embryo cryopreservation, although female age significantly affects outcomes in this system [50]. Embryo development is not affected by the vitrification procedure. The efficiency obtained up to the present time justifies the use of oocyte vitrification in the routine clinical work (e.g. to accumulate oocytes in preimplantation genetic diagnosis cycles).

The available evidence indicates that obstetric and perinatal outcomes in infants conceived from vitrified oocytes do not appear to be associated with adverse outcomes [41] nor with apparent increase in congenital anomalies [51].

The most widely emphasized concerns in the vitrification process are toxicity and danger of contamination. Unfortunately, available vitrification methods still struggle with these problems today [52]. However, in most vitrification methods, the time of exposure to the final cryoprotectant concentrations is very limited at temperatures where this toxic effect may still be significant (above 20 °C to −40 °C). Recent vitrification techniques have shown that UV irradiation is feasible for rapid microbial decontamination of liquid nitrogen [53].

Although a standardized vitrification protocol has not yet been defined, vitrification has been used routinely in most IVF laboratories recently and good survival and pregnancy rate of embryos have been consistently achieved. Oocyte vitrification constitutes a realistic option for FP.

Ovarian tissue cryopreservation

The main advantage of ovarian tissue cryopreservation is that it can be rapidly performed, without delaying the oncological treatment and represents the only option for prepubertal girls. It requires a surgical procedure, usually done laparoscopically, in which ovarian cortical strips or one entire ovary is removed. Oophorectomies are usually performed in young girls or when the risk of ovarian failure is very high. Some teams remove one entire ovary systematically instead of cortical strips as it allows several transplantation attempts, without evidence suggesting that it has a major impact on the natural age-related decline in fertility.

Transportation of ovarian tissue on ice prior to cryopreservation has been reported by some authors and does not seem to have a negative impact on follicular viability [54], as pregnancy can occur [55].

Ovarian tissue in the form of thin cortical strips can be cryopreserved either by the slow-freezing technique or by vitrification. Up to now, all pregnancies come from grafts that were previously cryopreserved by the slow-freezing technique. The standard method of human ovarian cryopreservation is slow-programmed freezing [56] but recent data suggest that vitrification could be more effective [57]. A recent study evaluated the impact of slow freezing and vitrification procedures on oocyte survival rates in 16 cancer patients. The viability of oocytes from slow-freezing specimens was 42% compared to 92% of oocyte survival from vitrified specimens ($p < 0.01$) [58].

Options to restore fertility from cryopreserved ovarian tissue include ovarian tissue autotransplantation and *in vitro* follicular maturation.

Ovarian tissue transplantation

Transplantation of ovarian cortical fragments can either be done orthotopically (whenever transplantation is done in the peritoneal cavity, this is the preferred option) or heterotopically (forearm or

anterior abdominal wall, probably associated with poorer oocyte quality due to inadequate environment). Neoangiogenesis after ovarian tissue transplantation is still the limiting factor as it takes five days and leads to 60% loss of primordial follicles; regarding this issue, grafting the tissue into the remaining bleeding ovarian medulla is of great importance to restore vascularization. Long duration of the graft has been described for both orthotopic and heterotopic sites (longest duration 54 months) but despite this fact, fertility remains low probably due to the perimenopausal environment of the remaining ovary [59].

Fresh and frozen cortical ovarian tissue transplantations have been successfully reported worldwide, resulting in around 28 healthy babies [58]. Reported pregnancies up to date have been both spontaneous and after IVF [60,61].

Assisted reproduction may be used in order to optimize chances of pregnancy and these patients should always be considered as poor responders [62].

Ovarian tissue transplantation has the potential advantage of restoring not only fertility but also the ovarian endocrine function. Reporting of the procedure in order to develop a registry and get to know the real efficacy of the technique is of great importance.

Whole ovary transplantation with its vascular pedicle remains an experimental procedure in humans [63–65]. It has the theoretical advantage of avoiding the initial ischemia period that leads to follicle depletion, however, cannulation of the pedicle and microsurgical anastomosis are technically difficult, with a high risk of thrombosis after anastomosis; additionally, adequate diffusion of cryoprotectant agents to the whole tissue is still a limiting step.

Ovarian tissue cryopreservation and transplantation should no longer be considered an experimental strategy for FP; currently, the best available option is to cryopreserve ovarian cortical strips by slow freezing and transplant them orthotopically. Autotransplantation of ovarian tissue in women who have suffered from hematological malignancies is not recommended because of the high risk of retransmission of malignancy [62].

IVM of follicles

Despite promising results, transplantation of frozen–thawed ovarian tissue is not advisable for patients with certain types of cancer as there is risk of reintroducing malignant cells. In these cases, *in vitro* follicle maturation, which is still an experimental procedure, could be a safer alternative.

To grow follicles and oocytes *in vitro*, there are two main options: isolated follicle culture or *in situ* follicle growth. Isolated follicle culture is very difficult and culture conditions are not affordable. *In situ* follicle culture can be performed in whole ovary or cortical ovarian strips, in membrane inserts or xenotransplanted. Growing follicles *in vitro* constitutes a big challenge, since in humans follicle growth from primordial to preantral stages takes up 6–9 months. Several protocols for follicular isolation (use of enzymes or mechanical skills) and culture conditions (addition or not of gonadotrophins to culture medium) have been described by different groups around the world [66–68]. It is important to take into account the biological risks of IVM of oocytes due to epigenetic disorders that may occur during culture.

Follicle culture for FP can be an option but first it is necessary to assess normal embryo development and the follow up of the offspring derived from *in vitro* cultured follicles and *in vitro* matured oocytes.

Ethical, social and psychological aspects of FP

Existing literature suggests that most cancer survivors emphasize the need for health professionals to be clear and provide realistic information when addressing the risk for infertility associated with cancer treatment regimens. Survey studies have shown that cancer does not influence the desire for pregnancy in 71% of women and 68% of men [69]. Despite this, current possibilities of FP are not always offered in the large majority of potential candidates. Counseling should offer support for patients and provide better care by understanding emotional needs, psychological predictors of distress and methods of coping. Unrealistic expectations of success should not be given in any case. It is also necessary to determine how long the storage period needs to be, if it should be variable depending on the patient's age, how often has the consent form to be renewed and other practical questions. Furthermore, it is important to ensure good medical practice to prevent cancer recurrence. Development of guidelines to safeguard the ethical principles of autonomy, non-maleficence, justice and equity as well as a registry of fecundity measures undertaken in cancer patients at a national level [70,71] are necessary to be able to assess the results of this practice in the future.

Concluding remarks

Advances in diagnosis and treatment of cancer have led to increased survival rates of oncologic patients, therefore, long-term effects of cancer treatment, such as infertility, have become an important issue. Ovarian tissue cryopreservation is the only strategy for prepubertal girls while oocyte cryopreservation is the preferred option for postpubertal females. Choosing one or another will depend on multiple factors, as it has been previously mentioned, and nowadays there is a trend toward combining several strategies in order to maximize chances of success. Early referral to the fertility specialist is of great importance as FP may improve quality of life in these patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012;118:1710–7.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
3. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 2005;6:209–18.
4. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009;45:992–1005.
5. Scotting PJ, Walker DA, Perilongo G. Childhood solid tumours: a developmental disorder. Nat Rev Cancer 2005;5:481–8.
6. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975–2002, National Cancer Institute. Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER website, 2005; [Last accessed 27 Dec 2012].

7. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 2009;27:2308–18.
8. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 2003;290:1583–92.
9. Martín I, Valls C, Pavía C, et al. Gonadal function and puberty assessment in a cohort of Spanish pediatric survivors of childhood cancer. Endocrinologist 2009;19:133–41.
10. Cancer Research UK. Cancer Incidence by Age 2009. Available at: http://info.cancerresearchuk.org/cancerstats/ [Last accessed 27 Dec 2012].
11. Schmidt KT, Larsen EC, Andersen CY, Andersen AN. Risk of ovarian failure and fertility preserving methods in girls and adolescents with a malignant disease. BJOG 2010;117:163–74.
12. Hudson MM, Mulrooney DA, Bowers DC, et al. High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. J Clin Oncol 2009;27:2405–14.
13. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24:2917–31.
14. Broekmans FJ, Knauff EA, te Velde ER, et al. Female reproductive ageing: current knowledge and future trends. Trends Endocrinol Metab 2007;18:58–65.
15. Wallace WH, Kelsey TW. Human ovarian reserve from conception to menopause. PLoS ONE 2010;5:e8772.
16. Rosendahl M, Andersen CY, la Cour Freiesleben N, et al. Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age. Fertil Steril 2010;94:156–66.
17. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001;7:535–43.
18. Meirow D, Biederman H, Anderson RA, Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol 2010;53:727–39.
19. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2006;91:1723–8.
20. Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol 1999;17:2365–70.
21. Broekmans FJ, Kwee J, Hendriks DJ, et al. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006;12:685–718.
22. La Marca A, Sighinolfi G, Radi D, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010;16:113–30.
23. Lie Fong S, Lugtenburg PJ, Schipper I, et al. Anti-Müllerian hormone as a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies. Hum Reprod 2008;23:674–8.
24. Partridge AH, Ruddy KJ, Gelber S, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril 2010;94:638–44.
25. Anderson RA, Cameron DA. Pretreatment serum anti-Müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011;96:1336–43.
26. Greve T, Schmidt KT, Kristensen SG, et al. Evaluation of the ovarian reserve in women transplanted with frozen and thawed ovarian cortical tissue. Fertil Steril 2012;97:1394.1398.e.1.
27. Meirow D, Baum M, Yaron R, et al. Ovarian tissue cryopreservation in hematologic malignancy: ten years' experience. Leuk Lymphoma 2007;48:1569–76.
28. Wallace WH, Thomson AB. Preservation of fertility in children treated for cancer. Arch Dis Child 2003;88:493–6.
29. Norwitz ER, Stern HM, Grier H, Lee-Parritz A. Placenta percreta and uterine rupture associated with prior whole body radiation therapy. Obstet Gynecol 2001;98:929–31.
30. Critchley HO, Wallace WH. Impact of cancer on uterine function. J Natl Cancer Inst Monogr 2005;34:64–8, doi: 10.1093/jncimonographs/lgi022.
31. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. Oncologist 2007;12:1044–54.
32. Oktay K, Buyuk E, Libertella N, et al. 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.
33. Oktay K, Hourvitz A, Sahin G, 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.
34. Oktay K, Türkçüoğlu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online 2010;20:783–8.
35. Quintero RB, Helmer A, Huang JQ, Westphal LM. Ovarian stimulation for fertility preservation in patients with cancer. Fertil Steril 2010;93:865–8.
36. Garcia-Velasco JA. Agonist trigger: what is the best approach? Agonist trigger with vitrification of oocytes or embryos. Fertil Steril 2012;97:527–8.
37. Friedler S, Koc O, Gidoni Y, et al. Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis. Fertil Steril 2012; 97:125–33.
38. Bedoschi GM, de Albuquerque FO, Ferriani RA, Navarro PA. Ovarian stimulation during the luteal phase for fertility preservation of cancer patients: case reports and review of the literature. J Assist Reprod Genet 2010;27:491–4.
39. Oktay K, Demirtas E, Son WY, et al. In vitro maturation of germinal vesicle oocytes recovered after premature luteinizing hormone surge: description of a novel approach to fertility preservation. Fertil Steril 2008;89:228.e19–22.
40. Demirtas E, Elizur SE, Holzer H, et al. Immature oocyte retrieval in the luteal phase to preserve fertility in cancer patients. Reprod Biomed Online 2008;17:520–3.
41. Maman E, Meirow D, Brengauz M, et al. Luteal phase oocyte retrieval and in vitro maturation is an optional procedure for urgent fertility preservation. Fertil Steril 2011;95:64–7.
42. Chian RC, Huang JY, Gilbert L, et al. Obstetric outcomes following vitrification of in vitro and in vivo matured oocytes. Fertil Steril 2009;91:2391–8.
43. Cao YX, Chian RC. Fertility preservation with immature and in vitro matured oocytes. Semin Reprod Med 2009;27:456–64.
44. Parmegiani L, Bertocci F, Garello C, et al. Efficiency of human oocyte slow freezing: results from five assisted reproduction centres. Reprod Biomed Online 2009;18:352–9.
45. Kuwayama M, Vajta G, Kato O, Leibo P. Highly efficient vitrification method for cryopreservation of human oocytes. Reprod Biomed Online 2005;11:300–8.
46. Smith GD, Serafini PC, Fioravanti J, et al. Prospective randomized comparison of human oocyte cryopreservation with slow-rate freezing or vitrification. Fertil Steril 2010;94:2088–95.
47. Tulandi T, Huang JY, Tan SL. Preservation of female fertility: an essential progress. Obstet Gynecol 2008;112:1160–72.
48. Nagy ZP, Chang CC, Shapiro DB, et al. The efficacy and safety of human oocyte vitrification. Semin Reprod Med 2009;27:450–5.
49. Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2011;96:277–85.
50. Rienzi L, Romano S, Albricci L, et al. Embryo development of fresh 'versus' vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. Hum Reprod 2010;25:66–73.
51. Ubaldi F, Anniballo R, Romano S, et al. Cumulative ongoing pregnancy rate achieved with oocyte vitrification and cleavage stage transfer without embryo selection in a standard infertility program. Hum Reprod 2010;25:1199–205.
52. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online 2009;18:769–76.
53. Son WY, Tan SL. Comparison between slow freezing and vitrification for human embryos. Expert Rev Med Devices 2009;6:1–7.
54. Parmegiani L, Accorsi A, Cognigni GE, et al. Sterilization of liquid nitrogen with ultraviolet irradiation for safe vitrification of human oocytes or embryos. Fertil Steril 2010;94:1525–28.
55. Andersen CY, Rosendahl M, Byskov AG, et al. Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod 2008;23:2266–72.

56. Dittrich R, Lotz L, Keck G, et al. Live birth after ovarian tissue autotransplantation following overnight transportation before cryopreservation. Fertil Steril 2012;97:387–90.
57. Hovatta O. Methods for cryopreservation of human ovarian tissue. Reprod Biomed Online 2005;10:729–34.
58. Keros V, Xella S, Hultenby K, et al. Vitrification versus controlled-rate freezing in cryopreservation of human ovarian tissue. Hum Reprod 2009;24:1670–83.
59. Silber SJ. Ovary cryopreservation and transplantation for fertility preservation. Mol Hum Reprod 2012;18:59–67.
60. Rosendahl M, Schmidt KT, Ernst E, et al. Cryopreservation of ovarian tissue for a decade in Denmark: a view of the technique. Reprod Biomed Online 2011;22:162–71.
61. Donnez J, Silber S, Andersen CY, et al. Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med 2011;43:437–50.
62. Revel A, Laufer N, Ben Meir A, et al. Micro-organ ovarian transplantation enables pregnancy: a case report. Hum Reprod 2011;26:1097–103.
63. Grynberg M, Poulain M, Sebag-Peyrelevade S, et al. Ovarian tissue and follicle transplantation as an option for fertility preservation. Fertil Steril 2012;97:1260–8.
64. Martinez-Madrid B, Donnez J. Cryopreservation of intact human ovary with its vascular pedicle: or cryopreservation of hemiovaries? Hum Reprod 2007;22:1795.
65. Patrizio P, Gavish Z, Martel M, et al. Whole human ovaries cryopreservation using a novel multi-gradient freezing device. Fertil Steril 2007;88:S355.
66. Bedaiwy MA, Hussein MR, Biscotti C, Falcone T. Cryopreservation of intact human ovary with its vascular pedicle. Hum Reprod 2006;21:3258–69.
67. Harris SE, Adriaens I, Leese HJ, et al. Carbohydrate metabolism by murine ovarian follicles and oocytes grown in vitro. Reproduction 2007;134:415–424.
68. Newton H, Picton HM, Gosden RG. In vitro growth of oocyte–granulosa cell complexes isolated from cryopreserved ovine tissue. J Reprod Fertil 1999;115:141–150.
69. Picton HM, Harris SE, Muruvi W, Chambers EL. The in vitro growth and maturation of follicles. Reproduction 2008;136:703–15.
70. Schover LR, Brey K, Lichtin A, et al. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. J Clin Oncol 2002;20:1880–9.
71. de Ziegler D, Streuli I, Vasilopoulos I, et al. Cancer and fecundity issues mandate a multidisciplinary approach. Fertil Steril 2010;93:691–6.