EXPERT REVIEWS

Management of reproductive needs in cancer patients: clinical perspectives

Expert Rev. Anticancer Ther. 8(10), 1589–1595 (2008)

Mohamed F Mitwally
University of Minnesota Medical Center, Riverside Professional Building, 606 24th Avenue South, Suite 402, Minneapolis, MN 55454, USA
Tel.: +1 612 372 7016
Fax: +1 612 372 7015
mmitwally@yahoo.com

Over the last few decades, a growing number of cancer survivors cured or in long-term remission following successful cancer treatment, have particular reproductive health needs. Achieving or preventing pregnancies, as well as replacement of sex hormone deficiency are three main reproductive issues. Managing such reproductive needs requires a close collaboration between specialists in oncology, reproductive endocrinology and andrology. Currently, there are few collaborative efforts to bridge the gaps between these three subspecialties. Patients are often lost between oncologists who lack the interest in addressing reproductive issues, and reproductive endocrinologists and andrologists, who do not have the clinical practice model to provide emergency consultations for cancer patients or adequate follow-up. On the other hand, there is severe deficiency in patients' education and knowledge regarding the consequences of cancer treatment on their reproductive life and the available modern technologies in reproductive medicine. Perhaps the time has come to build a new medical subspecialty that can address and manage the long-term health needs of cancer survivors, including reproductive needs.

KEYWORDS: cancer survivor • chemotherapy • contraception • fertility preservation • radiotherapy • reproduction

This is the third in a series of three articles discussing cancer and human reproduction from a clinical perspective. The first article presented a general overview of how cancer and its treatment can adversely affect human reproduction, summarizing the nature and extent of those adverse effects in men, women and their offspring [1]. The second article discussed the different approaches to minimize the reproductive damage caused by cancer and its treatment, as well as the various options for preserving human fertility in cancer survivors [2]. This article discusses, from a clinical perspective, the management of three important reproductive needs for cancer survivors. First, fertility enhancement in women by ovarian stimulation and assisted reproduction when fertility is desired. Second, contraceptive needs when fertility is not desired. Third, replacement of hormonal deficiency, in particular delayed or absent puberty, menopause and andropause.

Recent advances in the early detection of cancer and its effective treatment have resulted in a growing number of cancer survivors worldwide. The National Cancer Institute and the Centers for Disease Control and Prevention estimated that there were more than 10 million cancer survivors in the USA alone, in 2002. With current figures predicting that 60% of adults newly diagnosed with cancer are expected to be alive 5 or more years later, out of the 1,300,000 new cancer cases anticipated in 2006 in the USA, almost 0.8 million individuals will survive cancer. This number is still growing and the projected incidence of new cancer cases in the USA in 2007 was almost 1,500,000 (up from 1,300,000 in 2006) with approximately 4% of them expected to occur in patients younger than 35 years old. By 2010, it is estimated that one in every 250 people in the adult population (during their reproductive age) will be childhood cancer survivors [3,4].

In a recent review, Carver *et al.* investigated the late effects of cancer treatment, focusing on cardiac and pulmonary late consequences in cancer survivors. The authors concluded that the cancer and its treatment have a substantial impact on the long-term health of cancer survivors, including organ damage and functional disabilities, as well as the problem of the

 10.1586/14737140.8.10.1589 ISSN 1473-7140

development of second malignancies. Moreover, they highlighted the significance of the growing recognition that these late effects have become more common with the increasing use of more complex and intensive cancer treatment, with a growing number of cancer survivors [4].

Currently, there is a growing need to provide adequate long-term clinical care for cancer survivors that is dependent on evidence-based guidelines. Comprehensive long-term clinical care would not be complete without including the important reproductive issues that cancer survivors might have, including desired fertility, contraceptive needs and hormone-replacement therapy. There are helpful guidelines addressing long-term health problems in cancer survivors including recommendations from experts in the area [101].

Cancer survivors desiring fertility

Ovarian stimulation & assisted reproductive technology

For those cancer survivors desiring fertility, options depend on two main factors: extent of gonadal damage and gender. With complete gonadal damage, third-party assisted reproductive technology (ART) is the only available option. This includes sperm and oocyte donors. With incomplete gonadal damage (i.e., when the sperm production or ovarian reserve is severely impaired), the outcome of fertility treatment is significantly gender dependent. While ART with intracytoplasmic sperm injection is highly successful for cases of severe sperm depletion, the case is different for women. With significant reduction of ovarian reserve, the outcome of ART is usually not encouraging unless oocytes are obtained from healthy young oocyte donors. Several approaches have been tried to improve ovarian reserve, but without promising outcomes [5].

It is important to mention here that in all cases of hereditary/familial cancer survivors, the option of preimplantation genetic diagnosis (PGD) with ART should be offered to cancer survivors. This option should also be offered to other family members who could be carrying a genetic mutation that would predispose them or their offspring to the increased risk of suffering from such hereditary/familial cancer. With PGD, testing the embryos for the presence of a cancer-predisposing mutation can help to avoid the transmission of such a mutation into future offspring. This type of strategy might be successful in the eradication of many hereditary/familial cancers in the future. This issue will be discussed in more detail later.

In addition to the established ARTs, other experimental options are now available since the report of the first case of a spontaneous conception more than 5 years ago. This was in a young woman with documented ovarian failure in whom ovarian cortical tissue had been cryopreserved [6].

Low ovarian reserve in cancer patients

Ovarian reserve or the ability of the ovaries to produce good quality oocytes that can successfully fertilize and form a competent embryo that will implant and result in a healthy baby, is frequently impaired by cancer and its treatment [1,7]. One in every six female survivors was found to develop premature ovarian failure. Other survivors, with spontaneous menstrual cycles, usually have diminished ovarian reserve [8].

In a more recent study, which included 2819 survivors of childhood cancer aged 18 years or older, risk factors for premature menopause were found to include attained age, exposure to increasing doses of radiation to the ovaries, use of alkylating agents and a diagnosis of Hodgkin's lymphoma. For survivors who were treated with alkylating agents plus abdominopelvic radiation, the authors found that the cumulative incidence of premature menopause approached 30% [9].

The nonrenewable pool of ovarian primordial follicles declines, by atresia, from 2 million at birth to 500,000 at menarche. When the total number reaches 25,000 at a mean age of 37–38 years, the loss accelerates and spontaneous and assisted conceptions become increasingly difficult [10].

Although there are different methods to test for ovarian reserve, none of them is of proven superiority in all situations [1]. The most important test believed to determine the extent of ovarian reserve is to stimulate the ovaries with fertility medications and test the ability of the obtained oocytes to fertilize and result in healthy pregnancy. When reduced ovarian reserve is suspected, it is crucial not to delay fertility treatment for investigating the ovarian reserve. The most logical approach is to start administering fertility medications (ovarian stimulation) when deemed safe and try to achieve pregnancy without delay. This is important, as the window of chance for a cancer survivor might be too short to waste while waiting for further investigations and laboratory work-up.

Regain of ovarian reserve

As suggested previously, delaying in fertility treatment pending investigation of ovarian reserve is not clinically warranted. Such an approach is supported by the general belief among reproductive endocrinologists that once ovarian reserve has deteriorated, it is almost never back to normal again. However, it is believed that the decline in ovarian reserve does not follow a steady sloping decline path. On the contrary, sometimes the recovery of some ovarian reserve may happen over time either spontaneously or with treatment. In support of this hypothesis, some women with premature ovarian failure were reported to regain some ovarian function after being in menopause for several months, experiencing spontaneous ovulations and even pregnancy [11]. Moreover, there are interesting recent reports of some breast cancer survivors suffering from iatrogenic menopause, who were found to regain some of their ovarian hormonal function and even ovulate and achieve pregnancy after using aromatase inhibitors [12].

Ovarian stimulation in cancer patients

Ovarian stimulation is usually applied, particularly in conjunction with ART, to achieve multiple oocyte development to enhance the chances of success of infertility treatment. High estrogen levels are inevitably attained during ovarian stimulation because each of the growing ovarian follicles will be contributing to estrogen production, leading to the achievement of supraphysiological levels of estrogen. High levels of estrogen

are not desirable, particularly in women who have survived estrogen-dependent cancers (particularly breast and endometrial cancer). The aromatase inhibitors are estrogen-suppressing agents that have been approved for women with breast cancer and have been reported recently to be successful for ovarian stimulation either alone or with gonadotropins. Interestingly, with the use of aromatase inhibitors for ovarian stimulation, multiple ovarian follicular development has been associated with significantly lower estrogen levels compared with ovarian stimulation with gonadotropins alone [13–15]. For this reason, aromatase inhibitors have been suggested to stimulate ovulation in breast cancer survivors [16,17]. Recently, reports of successful use of the aromatase inhibitors for ovarian stimulation in cancer survivors have been accumulating [18–22].

Concerns regarding pregnancy outcome after the off-label use of the aromatase inhibitors for ovarian stimulation have been refuted by recent reports on the safety of pregnancy outcome in babies delivered following stimulation by aromatase inhibitors. The short half-life of the aromatase inhibitors enables their complete clearance from the body before the implantation period, thus reducing the likelihood of detrimental effects on the pregnancy [23,24].

Pregnancy after cancer treatment

This topic, including the safety of pregnancy on the mother and health of babies born, has been discussed previously in the first two manuscripts of this series [1,2]. Edgar and Wallace have reviewed this topic in their recent review with reference to a number of large, multicenter studies that are underway and will provide new insights into pregnancy outcomes in survivors of childhood cancer [25].

Gestational carrier is an option in situations when a cancer survivor cannot undergo pregnancy due to surgical absence of the uterus or the presence of a uterus with a blood supply damaged by cancer treatment, such as post-radiation. This is also true when the cancer survivor cannot undergo pregnancy due to general health problems [2]. With this option, embryos can be created by fertilizing the oocytes from the cancer-surviving woman using her partner's sperm *in vitro*, then transferring the embryo into the uterus of another woman (gestational carrier). This option is valid for frozen embryos and/or oocytes obtained before cancer treatment when the cancer survivor cannot achieve pregnancy.

Breastfeeding after cancer treatment

There is inadequate literature on breastfeeding in women surviving cancer treatment. Most of the available literature includes sporadic case reports on breastfeeding in women who have survived breast cancer. The two issues that have been identified as important for women who breastfeed after breast cancer are: the mechanical ability to breastfeed after cancer treatment (radiation treatment [26,27] and breast surgery) and the risk of activating breast cancer by breastfeeding, despite literature indicating the contrary (i.e., that breastfeeding protects against breast cancer). Small case studies have documented the success of breastfeeding from an affected breast. However, some difficulties have been experienced, such as the infant favoring the nonaffected breast and low milk supply [28–30]

ART with PGD for hereditary cancers

With recent advances in cancer genetics, there is a growing list of genetic mutations associated with hereditary cancers and predisposition for cancer, such as *BRCA1* and *BRCA2* association with breast and ovarian cancer. It is important to counsel survivors of these cancers regarding the technology of PGD, which would allow the selection of embryos free from the mutations. This will almost eliminate the risk of passing those genetic mutations onto the offspring and minimize their risk of developing such hereditary cancers. The PGD program requires collaboration between the ART team, clinical geneticists and laboratory investigators [31].

The success of PGD appears to approximately follow the general success rates ART with success rates of achieving a healthy live-birth of approximately 25% per treatment cycle. Examples of the conditions that benefit from PGD include adenomatous polyposis coli, *BRCA*, retinoblastoma, Li–Fraumeni syndrome and von Hippel–Lindau syndrome, as well as disorders that predispose to cancer (Fanconi anemia, Wiskott–Aldrich syndrome) [32]. The list of such hereditary cancer predisposition syndromes is long and likely to increase [33].

It is important to mention here that the ethical dilemma regarding embryo selection by PGD has been the topic of intense debate. However, there is an acceptable consensus that, except for sex selection of the child, most current extensions of PGD are ethically acceptable [34].

Contraceptive needs for cancer survivors

For women surviving cancer treatment who still have fertility potential following cancer treatment but do not desire achieving pregnancy or for whom pregnancy is contraindicated, an effective method of contraception is needed. These women can be divided into three groups. The first group includes women for whom pregnancy is permanently undesired or contraindicated. The second group includes women for whom pregnancy is temporarily contraindicated (due to adverse effects expected from high sex hormones associated with pregnancy), such as survivors of breast cancer or other estrogen-dependent cancers, such as endometrial cancer. The third group includes women for whom pregnancy is temporarily contraindicated without concern about the high sex hormones levels associated with pregnancy. For this group, most available methods of contraception can be considered.

For the first group when fertility is permanently undesired or pregnancy is permanently contraindicated, a safe method of sterilization is a good choice, including tubal interruption by ligation through laparoscopy or minilaparotomy. For those with contraindication for laparoscopy or laparotomy, the option of hysteroscopic sterilization is an exciting new effective method of sterilization that has the advantage of effectiveness with less invasiveness [35].

For the second group of women, for whom pregnancy is temporarily contraindicated due to the concern regarding the high sex hormone levels associated with pregnancy, such as survivors of breast cancer and possibly hepatocellular carcinoma and cholangiocarcinoma, postponing pregnancy until a disease-free interval of 3–5 years has been achieved is recommended. Nonhormonal contraceptives are the appropriate choice [35].

Hormonal replacement therapy for cancer survivors

A significant number of cancer survivors, both males and females, suffer from sex hormonal deficiency (andropause and menopause respectively) due to the surgical extirpation of the gonads or as a result of cancer treatment (chemotherapy and/or radiotherapy) [36]. A recent follow-up on the function of the hypothalamic–pituitary–gonadal axis in long-term survivors of hematopoietic stem cell transplantation for hematological diseases included a series of 41 female and 31 male patients who had undergone bone marrow/peripheral blood stem cell transplantation at a mean age at transplantation of 32.6 years and mean follow-up interval from transplantation of 1.5 years (range: 0.2–9.8 years). Although none of the patients had gonadal dysfunction prior to their underlying illness, hypergonadotrophic hypogonadism was observed in almost all females (97%) and a good proportion of males (19%). In 32% of males, despite normal testosterone levels, evidence of Leydig cell strain (normal testosterone, high luteinizing hormone levels) was present. Moreover, spermatogenesis damage (high follicle-stimulating hormone levels) was observed in two-thirds of the males (68%) [37].

A more recent study included, in a cross-sectional design, 176 male cancer survivors and 213 male controls, aged 25–45 years. Of the cancer survivors, 97% had received chemotherapy and 40% radiotherapy. The authors found cancer survivors had significantly lower total testosterone than controls. Cancer survivors had features of hypogonadism, including a greater fat mass, higher fasting insulin and glucose levels, increased fatigue and reduced sexual function and health-related quality of life [38].

For these patients, the nature of their cancer, as well as the severity of symptoms of hormonal deficiency are the two main determinants of the decision for starting and choosing the hormone-replacement regimens. A third important determinant of the decision for sex hormone-replacement therapy, which is unfortunately usually overlooked, includes long-term health problems associated with premature loss of the gonadal hormonal function. These long-term health problems include, in particular, the risks of bone loss and fractures and possible cardiovascular problems, such as coronary artery disease and hypertension. Balancing the risks of activating underlying sex hormone-sensitive cancers against the risks of sex hormone deficiency is a very difficult clinical question. This is well illustrated in young women who survive breast cancer. In these patients, nonhormonal options to relieve menopausal symptoms have been tried. In a recent systematic review of therapeutic options for the treatment of menopausal symptoms in cancer survivors, the authors reviewed both pharmacological and nonpharmacological options. The authors found that despite the availability of a number of nonpharmacologic approaches, those approaches did not appear to be of significant value. On the other hand, complementary alternative medicine therapies and vitamin E were found to have modest effectiveness at best, with a lack of data on their long-term safety. The approaches that were found to be of significant clinical effectiveness and well tolerated included centrally active agents, such as the antidepressants venlafaxine and paroxetine, and the antiseizure agent gabapentin [39].

In a recent review concerning testosterone-replacement therapy for andropause, Morgentaler evaluated the issue of testosterone therapy for men at risk for or with history of prostate cancer [40]. The author indicates that because of the assumption that higher testosterone levels cause enhanced growth of prostate cancer, it has been considered taboo to offer testosterone-replacement therapy to any man with a prior history of prostate cancer, even if all objective evidence suggests he has been cured. Furthermore, the US FDA mandated language in all testosterone package inserts state that testosterone is contraindicated in men with a history of or suspected of having prostate cancer due to the fear that higher testosterone levels would 'awaken' dormant cells and cause a recurrence. The review challenges the taboo of testosterone-replacement therapy because of the lack of experience with prostate cancer activation due to administration of testosterone in men with known history of prostate cancer. On the contrary, there is extensive literature indicating that testosterone replacement does not pose any increased risk of prostate cancer growth in men with or without prior treatment. Further evidence discussed by the review article is that prostate cancer is almost never observed in the peak testosterone years of the early 20s, despite autopsy evidence that men in this age group already harbor microfoci of prostate cancer in substantial numbers. Moreover, there has been a report on the absence of prostate-specific antigen recurrence with testosterone replacement in small numbers of men after radical prostatectomy. The author concluded that although still controversial, there appears to be little reason to withhold testosterone-replacement therapy from men with favorable outcomes after definitive treatment for prostate cancer. For those men on testosterone replacement, monitoring with prostate-specific antigen and digital rectal examination at regular intervals is recommended [40].

To conclude, the issue of hormone-replacement therapy for hormonal deficiency following cancer treatment remains an extremely controversial issue that needs further extensive research to aid decision-making, balancing the risk of activating underlying sex hormone-dependent cancers against the short- and long-term health benefits of sex hormone-replacement therapy. Mulder addressed the issue in an interesting review that focused on young adult cancer survivors [41].

Pubertal disturbance following cancer treatment

Cancer treatment can affect puberty in different ways. Both precocious and delayed puberty can occur as a result of disturbance of the hypothalamic–pituitary–gonadal axis. Gonadal damage may

result in delayed puberty or even absent puberty when the damage is irreversibly complete. Müller reviewed the issue of pubertal disturbances associated with cancer treatment. Chemotherapy and irradiation of the brain given for childhood cancer can affect the hypothalamic–pituitary–gonadal axis, which carries the risk of late endocrine effects, including pubertal disturbances. Cranial irradiation during the prepubertal age can induce early or even precocious puberty, particularly in girls. Damage to the hypothalamic–pituitary axis may cause hypogonadotrophic hypogonadism at a later stage. Gonadal damage secondary to irradiation, such as part or total body irradiation before bone marrow transplantation, will most likely cause gonadal failure and incomplete or absent puberty in girls. Interestingly, this is not the case in boys who in most cases will experience normal pubertal development except for small testes. Gonadal damage can also occur secondary to chemotherapy, particularly when alkylating agents are administered, which are particularly gonadotoxic. Again, girls are more susceptible to gonadal failure than boys, who will usually achieve normal pubertal development. Unfortunately, a good proportion of childhood cancer patients receive a combination of cancer treatments that complicates the prediction of pubertal development [42].

The management of pubertal disturbances associated with cancer treatment should start with the careful close follow-up of these children following cancer treatment to detect any pubertal disturbances (either precocious or delayed). Treatment of precocious puberty due to premature activation of the hypothalamic-pituitary–gonadal axis should be amenable for treatment with GnRH analog. However, there is a paucity of information in the literature concerning outcomes, particularly in cancer patients [43].

On the other hand, delayed or absent puberty development should respond to sex hormone-replacement therapy. In addition, the use of growth hormone-replacement therapy is also of significant help [44,45]. However, there is no consensus with regard to when to start treatment, particularly in girls, and the best dosage and regimens of replacement therapy. Close teamwork between pediatric endocrinologists, reproductive endocrinologists and oncologists should help in achieving adequate clinical outcomes [46–53].

In addition to reproductive endocrine disruption associated with cancer and its treatment, other endocrine glands are affected.

Conclusion

There is an increasing need to provide adequate clinical care for reproductive needs to cancer survivors, whose numbers are growing every year. For those desiring fertility (i.e., achievement of pregnancy), preventing reproductive damage by cancer treatment, as well as fertility preservation before starting cancer treatment are believed to be the most effective approaches. However, the existence of successful ARTs provides promising hope for those who have already suffered from reproductive damage due to cancer treatment. For those who desire fertility, applying the technology of assisted reproduction with PGD to prevent the transmission of genetic mutations that predispose for hereditary cancers into their offspring is an exciting new technology. For fertile cancer survivors, preventing pregnancy by effective contraception is crucial when pregnancy is contraindicated. When sex hormonal deficiency is inevitably attained (premature menopause and andropause), balancing the risks of activating underlying cancers that are sex hormone dependent against the risks of long-term morbidity due to sex hormonal deficiency is usually a difficult clinical judgment. Adequate counseling by providing the available different options and risks is usually helpful in making a decision, which should be shared by the patient and the treating physician. A collaborative consultation between subspecialists in oncology, reproductive endocrinology and andrology should provide the best evidence-based clinical care for cancer survivors.

Expert commentary

There remain unmet needs for providing adequate long-term healthcare, particularly reproductive care, for patients surviving cancer treatment during their childhood and reproductive years. The lack of adequate patient counseling and failure of effective collaboration between subspecialists in oncology, reproductive endocrinology and andrology are the two major factors contributing to the failure to provide clinical reproductive care for cancer survivors. With growing numbers of cancer survivors every year, the time has come to consider building up a new medical subspecialty for reproductive endocrine–oncology that includes healthcare providers who have adequate clinical training and knowledge in reproductive issues related to cancer patients, including fertility preservation, hereditary oncogenetics and endocrine care for cancer patients.

Five-year view

The success of the new technologies of fertility preservation and reproductive genetics (PGD) in association with increasing demands from growing numbers of cancer survivors will open the door for the creation of a subspecialty of reproductive endocrine–oncology. Increased awareness of the available new technologies on the sides of both the healthcare professionals and patients should help in reducing the recent legislations and restrictions imposed on the practice of assisted reproduction in Europe and other parts of the world such as restrictions on oocyte and embryo freezing and practices of PGD. The expansion and high success of fertility preservation, assisted reproduction and PGD technologies will make these technologies more readily available and less expensive, which will lead to more patients benefiting from them.

Financial & competing interests disclosure

Mohamed F Mitwally has patents on the use of aromatase inhibitors for infertility treatment.

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Early detection of cancer and effective treatment make the number of cancer survivors grow every year worldwide. These cancer survivors need particular care for their long-term health problems, including reproductive health issues.
- The three main reproductive health issues include fertility desire (achieving pregnancy), preventing pregnancy (contraceptive needs) and sex hormone replacement (premature menopause and andropause).
- Preventing fertility damage and preserving fertility capacity are the best strategies for cancer patients undergoing cancer treatment. However, the availability of successful assisted reproductive technologies can still provide a hope for cancer survivors who suffer from reproductive damage from cancer treatment.
- Avoiding the transmission of hereditary cancers to the offspring by assisted reproduction and preimplantation genetic diagnosis is an exciting option for cancer survivors desiring fertility.
- Balancing sex hormonal administration to prevent long-term health problems caused by premature menopause and andropause and the risk of activating underling sex hormone-dependent cancers is a difficult clinical judgment that requires adequate counseling with patients.
- The wide gap between subspecialists in oncology, reproductive endocrinology and andrology is the basis for the lack of adequate reproductive care for cancer survivors.
- The time has come to consider establishing the subspecialty of reproductive endocrine–oncology to provide adequate clinical care for cancer survivors.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

▶1 Mitwally MF. Effect of cancer and cancer treatment on human reproduction. *Expert Rev. Anticancer Ther.* 7, 811–822 (2007).

•• **First of a three-article series reviewing the effect of cancer and its treatment on human reproduction. It outlines how cancer and its treatment can negatively affect reproduction in both males and females and the various mechanisms involved in such a negative impact.**

2 Mitwally MFM. Fertility preservation and minimizing reproductive damage in cancer survivors. *Expert Rev. Anticancer Ther.* 7, 989–1001 (2007).

•• **Second of a three-article series reviewing the effect of cancer and its treatment on human reproduction. It discusses the different approaches to minimize the reproductive damage caused by cancer and its treatment, as well as the various options for preserving human fertility in cancer survivors.**

3 Jemal A, Siegel R, Ward E *et al.* Cancer statistics, 2007. *CA Cancer J. Clin.* 57, 43–66 (2007).

•• **Updated information on the statistics and epidemiology of different cancer diagnoses.**

▶4 Carver JR, Shapiro CL, Ng A *et al.* American Society of Clinical Oncology Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects. *J. Clin. Oncol.* 25, 3991–4008 (2007).

•• **Comprehensive recent review article that addresses the importance of long-term care for cancer survivors and discusses the pulmonary and cardiac late effects following cancer treatment.**

5 Shanbhag S, Aucott L, Bhattacharya S, Hamilton MA, McTavish AR. Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in *in-vitro* fertilisation (IVF). *Cochrane Database Syst. Rev.* (1), CD004379 (2007).

▶6 Bath LE, Tydeman G, Critchley HOD, Anderson RA, Baird DT, Wallace WHB. Spontaneous conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis. *Hum. Reprod.* 19(11), 2569–2572 (2004).

7 Wallace WH, Anderson RA, Irvine DI. Fertility preservation for young people with cancer: who is at risk and what can be ▶offered? *Lancet Oncol.* 6, 209–218 (2005).

▶8 Larsen EC, Müller J, Schmiegelow K, Rechnitzer C, Andersen AN. Reduced ovarian function in long-term survivors of radiation and chemotherapy-treated childhood cancer. *J. Clin. Endocrinol. Metab.* 88, 5307–5314 (2003).

9 Sklar CA, Mertens AC, Mitby P *et al.* Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J. Natl Cancer Inst.* 98(13), 890–896 (2006).

10 Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum. Reprod.* 7, 1342–1346 (1992).

11 Santoro N. Mechanisms of premature ovarian failure. *Ann. Endocrinol. (Paris)* 64(2), 87–92 (2003).

12 Hargis JB, Nakajima ST. Resumption of menses with initiation of letrozole after five years of amenorrhea on tamoxifen: caution needed when using tamoxifen followed by aromatase inhibitors. *Cancer Invest.* 24(2), 174–177 (2006).

▶13 Mitwally MFM, Casper RF. Potential of aromatase inhibitors for ovulation and superovulation induction in infertile women. *Drugs* 66(17), 2149–2160 (2006).

▶14 Mitwally MFM, Casper RF. Letrozole for ovulation induction. *Expert Rev. Obstet. Gynecol.* 1(1), 15–27 (2006).

15 Casper RF, Mitwally MFM. Aromatase inhibitors for ovulation induction. *J. Clin. Endocrinol. Metab.* 91(3), 760–771 (2006).

16 Mitwally MFM, Casper FR. Using aromatase inhibitors to induce ovulation in breast Ca survivors. *Contemp. Ob. Gyn.* 49(1), 73–83 (2004).

17 Mitwally MFM, Casper RF. Preventing breast cancer with aromatase inhibition. *Contemp. Ob. Gyn.* 48(12), 68–80 (2003).

18 Azim AA, Costantini-Ferrando M, Lostritto K, Oktay K. Relative potencies of anastrozole and letrozole to suppress estradiol in breast cancer patients undergoing ovarian stimulation before *in vitro* fertilization. *J. Clin. Endocrinol. Metab.* 92(6), 2197–2200 (2007).

▶19 Azim A, Oktay K. Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma. *Fertil. Steril.* 88(3), 657–664 (2007).

▶20 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.* 91, 3885–3890 (2006).

▶21 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.* 23, 4347–4353 (2005).

22 Oktay K, Buyuk E, Davis O, Yermakova I, Veek L, Rozenwaks Z. Fertility preservation in breast cancer patients: *in vitro* fertilization and embryo cryopreservation after ovarian stimulation with tamoxifen. *Hum. Reprod.* 18, 90–95 (2003).

23 Mitwally MFM, Bilijan M, Casper RF. Pregnancy outcome after the use of an aromatase inhibitor for induction of ovulation. *Am. J. Obstet. Gynecol.* 192(2), 381–386 (2005).

24 Tulandi T, Martin J, Al-Fadhli R *et al.* Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertil. Steril.* 85(6), 1761–1765 (2006).

- **Number of large multicenter studies are underway and will provide new insights into pregnancy outcomes in survivors of childhood cancer.**

25 Edgar AB, Wallace WH. Pregnancy in women who had cancer in childhood. *Eur. J. Cancer* 43(13), 1890–1894 (2007).

26 Connell S, Patterson C, Newman B. A qualitative analysis of reproductive issues raised by young Australian women with breast cancer. *Health Care Women Int.* 27, 94–110 (2006).

27 Petrek JA. Breast cancer during pregnancy. *Cancer* 74, 518–527 (1994).

28 Neifert M. Breastfeeding after breast surgical procedure or breast cancer. *NAACOGS Clin. Issu. Perinat. Womens Health Nurs.* 3(4), 673–682 (1992).

29 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *Lancet* 360, 187–195 (2002).

30 Higgins S, Haffty BG. Pregnancy and lactation after breast-conserving therapy for early stage breast cancer. *Cancer* 73(8), 2175–2180 (1994).

31 Geraedts JP, Harper J, Braude P *et al.* Preimplantation genetic diagnosis (PGD), a collaborative activity of clinical genetic departments and IVF centres. *Prenat. Diagn.* 21, 1086–1092 (2001).

32 Simpson JL, Carson SA, Cisneros P. Preimplantation genetic diagnosis (PGD) for heritable neoplasia. *J. Natl. Cancer Inst. Monographs* 34, 87–90 (2005).

33 Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J. Clin. Oncol.* 23(2), 276–292 (2005).

34 Robertson JA. Extending preimplantation genetic diagnosis: the ethical debate. *Hum. Reprod.* 18(3), 465–471 (2003).

35 Temizkan M, Ouwendijk JT, Middelkoop MP, Blankenstein M, ten Kate FJ, Tytgat GN. A young female with a cholangiocarcinoma in the past: is pregnancy allowed? *Acta Gastroenterol. Latinoam.* 26(1), 31–34 (1996).

36 Critchley HO, Wallace WH. Do survivors of childhood cancer have increased incidence of premature menopause? *Nat. Clin. Pract. Oncol.* 4(2), 84–85 (2007).

37 Somali M, Mpatakoias V, Avramides A *et al.* Function of the hypothalamic-pituitary-gonadal axis in long-term survivors of hematopoietic stem cell transplantation for hematological diseases. *Gynecol. Endocrinol.* 21(1), 18–26 (2005).

38 Greenfield DM, Walters SJ, Coleman RE *et al.* Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. *J. Clin. Endocrinol. Metab.* 92(9), 3476–3482 (2007).

39 Goodwin M, Loprinzi C, Bordeleau L *et al.* Therapeutic options for the management of hot flashes in breast cancer survivors: an evidence-based review. *Clin. Ther.* 29(2), 230–241 (2007).

- **Recent comprehensive and interesting systematic review of the therapeutic options for the treatment of hot flashes in breast cancer survivors.**

40 Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. *Curr. Treat. Options Oncol.* 7(5), 363–369 (2006).

41 Mulder JE. Benefits and risks of hormone replacement therapy in young adult cancer survivors with gonadal failure. *Med. Pediatr. Oncol.* 33(1), 46–52 (1999).

42 Müller J. Disturbance of pubertal development after cancer treatment. *Best Pract. Res. Clin. Endocrinol. Metab.* 16(1), 91–103 (2002).

43 Adan L, Souberbielle JC, Blanche S. Adult height after cranial irradiation with 24 Gy: factors and markers of height loss. *Acta Paediatrica* 85, 1096–1101 (1996).

44 Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. *Endocr. Relat. Cancer* 11(4), 589–602 (2004).

45 Darzy KH, Pezzoli SS, Thorner MO, Shalet SM. The dynamics of growth hormone (GH) secretion in adult cancer survivors with severe GH deficiency acquired after brain irradiation in childhood for nonpituitary brain tumors: evidence for preserved pulsatility and diurnal variation with increased secretory disorderliness. *J. Clin. Endocrinol. Metab.* 90(5), 2794–2803 (2005).

46 Didcock V, Davies HA, Didi M. Pubertal growth in young adult survivors of childhood leukemia. *J. Clin. Oncol.* 13, 2503–2507 (1995).

47 Groot-Loonen JJ, van Setten P, Otten BJ. Shortened and diminished pubertal growth in boys and girls treated for acute lymphoblastic leukaemia. *Acta Paediatrica* 85, 1091–1095 (1996).

48 Hokken-Koelega CS, van Doorn WD, Hählen K. Long-term effects of treatment for acute lymphoblastic leukemia with and without cranial irradiation on growth and puberty; a comparative study. *Pediatr. Res.* 33, 577–582 (1993).

49 Melin E, Adan L, Leverger G. Growth hormone secretion, puberty and adult height after cranial irradiation with 18 Gy for leukaemia. *Eur. J. Pediatr.* 157, 703–707 (1998).

50 Moëll C, Marky I, Hovi L. Cerebral irradiation causes blunted pubertal growth in girls treated for acute leukemia. *Med. Pediatr. Oncol.* 22, 375–379 (1994).

51 Moell C, Garwicz S, Westgren U, Wiebe T. Disturbed pubertal growth in girls treated for acute lymphoblastic leukemia. *Pediatr. Hematol. Oncol.* 4, 1–5 (1987).

52 Mohnike K, Dorffel W, Timme J. Final height and puberty in 40 patients after antileukaemic treatment during childhood. *Eur. J. Pediatr.* 156, 272–276 (1997).

53 Maneschi F, Fugardi MG, Corsello G, LoCurto M. Pubertal maturation in girls treated for childhood acute leukaemia. *Eur. J. Pediatr.* 150, 630–633 (1991).

Website

101 Long-term follow up of survivors of childhood cancer. SIGN 76, January 2004 www.sign.ac.uk/guidelines/fulltext/76/index.html

Affiliation

- Mohamed F Mitwally, MD, HCLD, FACOG
Assistant Professor, Division of Reproductive Endocrinology & Infertility, Department of Obstetrics, Gynecology & Women's Health, University of Minnesota; University of Minnesota Medical Center, Riverside Professional Building, 606 24th Avenue South, Suite 402, Minneapolis, MN 55454, USA
Tel.: +1 612 372 7016; +1 612 372 7050
Fax: +1 612 372 7015; +1 612 372 7041
mmitwally@yahoo.com