

EDITORIAL



The female post-cancer fertility-counselling clinic: looking beyond the freezer. A much needed addition to oncofertility care

The number of girls and young women surviving cancer is increasing. It has been estimated that each year 43 new cancer cases are diagnosed per 100,000 people of both sexes between the ages of 20 and 39 years. Cancer is more common in women than men (Fidler *et al*, 2017). The consequences of being diagnosed with a malignant disease are serious, not just for the individual but also at a societal and economic level. While treatment is often successful, the impact of the disease on the life course is significant, as multiple long-term side effects of cancer treatment, and the psychological fallout of facing such a diagnosis at a young age, continue to resonate in later life. In a study based on the 2006 and 2010 LIVESTRONG surveys in which cancer survivors were contacted within 5 years following diagnosis, 89% of the respondents reported at least one physical concern and 90% reported at least one emotional concern, leading the authors to conclude that much work remains to be done to improve survivors' post-treatment care for physical, emotional and practical wellbeing (Beckjord *et al*, 2014). Other more long-term follow-up studies of childhood cancer survivors demonstrate multiple general health issues, such as cardiovascular morbidity, endocrine dysfunction or neurological sequelae (Geenen *et al*, 2007). It was concluded that post-treatment survivorship care is 'an active, complex and growing area of research and practice'.

POSSIBLE EFFECTS OF CANCER TREATMENT ON FERTILITY POTENTIAL

Clearly, one of the most serious side effects of cancer and its treatment for prepubertal girls is the risk of not entering puberty due to gonadal

damage and, for a young woman, the risk of premature menopause and the complete loss of future fertility potential (Meirow *et al*, 2010). Recognition of these serious side effects has led to increased focus and resources being dedicated to the field of fertility preservation over the last two decades. Many countries now have established programs for younger women diagnosed with cancer in their early reproductive years to ensure that they receive proper counselling regarding possible harm of cancer treatment to their future fertility and are offered fertility preservation if needed before they commence cancer treatment. It is important to emphasize that multi-disciplinary teams involving oncologists, fertility preservation coordinators, fertility specialists and so forth are needed in this context. Even today, in many countries a significant proportion of cancer patients embark on potentially gonadotoxic treatment without appropriate counselling regarding possible implications for future infertility and options to prevent this from happening.

Regularly offered fertility preservation techniques include embryo, oocyte or ovarian tissue cryopreservation, which can be performed before or, in case of ovarian tissue freezing, sometimes even during the course of gonadotoxic treatment (Donnez and Dolmans, 2017). For prepubertal girls, however, ovarian tissue cryopreservation is the only option to save eggs for future use (Dalle *et al*, 2017). The success of fertility preservation treatments in terms of live birth rate has been well-documented, with a success rate of approximately 33% following autotransplantation of cryopreserved ovarian tissue and the same for frozen embryo transfer of warmed and fertilized vitrified oocytes in cancer patients (Diaz-Garcia *et al*, 2018; Jensen *et al*, 2017). To

date, more than 130 children have been born after ovarian tissue cryopreservation and autotransplantation (Gellert *et al*, 2018).

There is no doubt that oncofertility programs are very much welcomed by cancer patients (Deshpande *et al*, 2015). Discussing fertility issues with a healthcare professional with special interest in fertility preservation is very important for young cancer patients and having 'eggs in the bank' may allow them to focus on other things during and after their treatment. And for many, it may represent the only hope of ever having a genetically 'own' child. With more and more centres around the world offering oncofertility services, more future cancer survivors will have embryos, oocytes or ovarian tissue in the freezer. Expert counselling and effective fertility preservation are now widely available for young women at the time of diagnosis, but what about afterwards? Does having eggs or ovarian tissue in the freezer mean that they no longer need counselling and care after having been cured?

NEED FOR FERTILITY-COUNSELLING CLINICS

In recent years there has been a growing interest in fertility clinics counselling men and women regarding their fertility potential, as opposed to the many existing family planning clinics whose sole purpose has been to provide advice concerning contraception (Hvidman *et al*, 2015). This need has arisen particularly in the western world as a consequence of delayed childbearing and the associated reduced fertility rates. Younger men and women can typically contact these clinics to have their fertility checked and receive counselling on whether it

TABLE 1 PROPOSAL FOR A COMPLETE ONCOFERTILITY SERVICE

Time point	Action
Cancer diagnosis	Patient is referred to a oncofertility specialist.
Fertility preservation counselling	Risk assessment and fertility preservation if needed.
Cancer treatment	Chemotherapy or radiation therapy.
6 months post-treatment	Fertility assessment (menstrual history, AMH, AFC). Discuss reproductive health issues.
12 months post-treatment	Fertility assessment (menstrual history, AMH, AFC). Discuss reproductive health issues. Plans for future pregnancy discussed.
24 months post-treatment	Fertility assessment (menstrual history, AMH, AFC). Discuss reproductive health issues.
>24 months post-treatment	Fertility assessment (menstrual history, AMH, AFC). Make use of cryopreserved gametes if necessary.

AFC = antral follicle count; AMH = anti-Müllerian hormone; FP = fertility preservation.

is safe to delay childbearing or whether they should start trying for a family soon. The aim is to help young couples to make informed decisions before it is too late.

We argue that for young female cancer survivors, fertility assessment and counselling is even more important as they are faced with a greater threat to their fertility due to the gonadotoxic treatment that many of them received previously. Apart from the worry of never being able to conceive with own eggs, these women are also concerned about the impact of the cancer treatment on their long-term health, including ovarian function. It is known that women with a pretreatment desire for children retain this desire years after their cancer diagnosis, and that failing to fulfill this desire is associated with worse mental health (*Armund et al, 2014*). Recently, it was suggested that survivors of adolescent and young adult cancer are a neglected group when it comes to long-term follow-up of physical (such as cardiovascular morbidity and endocrine diseases) and psychological (such as depression and post-traumatic stress disorder) sequelae of the cancer treatment itself (*Fidler et al, 2019*). And while multi-disciplinary late-effect clinics do exist in some countries, they are exclusively for childhood cancer survivors and not for women in their late twenties or thirties. The authors of the above study argued that the quality of survival must receive the same attention as the quantity of survival. This powerful statement demands a response from the oncofertility community too. We should join forces and aim for a more holistic and multi-disciplinary follow-up procedure.

FUTURE PERSPECTIVE FOR AN INTEGRATED COMPREHENSIVE ONCOFERTILITY SERVICE

We believe that the time has come for all centres offering oncofertility care to look beyond the freezer. Reproductive care for these women should also provide regular post-cancer follow-up visits for fertility assessment and counseling once the cancer treatment has ended. During such visits, other issues related to sexual and reproductive health should also be addressed such as sexual problems, which are common in patients previously treated for cancer (*Schover, 2018*), as well as the need for hormone replacement therapy. If the woman has a pregnancy wish and has failed to conceive, she can discuss the use of her cryopreserved gametes (oocytes, embryos or ovarian tissue) or donated gametes, and treatment plans can be made jointly with her and her oncologist to ensure optimal timing and safety. From the periconception perspective, it is important to optimize the health of women aiming to conceive to reduce the risk of complications during pregnancy and to secure the best possible future for the child. Ideally, such clinics should be multi-disciplinary and should, aside from fertility specialists, also include expertise from a range of other fields of medicine such as internal medicine, endocrinology, cardiology, psychology and so forth.

In **TABLE 1** we propose how a comprehensive oncofertility service could be structured, from the time of diagnosis until the patient has fulfilled

her desire for a family or no longer has a need for oncofertility care. We suggest the first visit for fertility assessment to be 6 months after the last course of chemotherapy, as it may take time for the ovaries to recover – if at all – from the detrimental effects of chemotherapy (*van der Kooi et al, 2019; Perdrix et al, 2017*). Furthermore, it is important to follow the patient for at least 24 months after chemotherapy, as an increase in serum anti-Müllerian hormone (AMH) concentration and the resumption of menstruation may be delayed for months or even years after the last course of chemotherapy (*Hamy et al, 2014*).

Assessing fertility potential may involve taking a menstrual history, measuring serum AMH concentration, and monitoring antral follicle count (AFC) by transvaginal ultrasound scan. At the follow-up visits, reproductive health issues such as sexual dysfunction or endocrine dysfunction can be discussed and treated if necessary. In those cases where there is a pregnancy wish, the patient can be counselled to aim for a spontaneous pregnancy or to proceed with her cryopreserved gametes depending on the findings of the fertility assessment.

To conclude, the time has come for oncofertility clinics to be an important and integrated part of cancer care to help patients towards a healthier and happier life after cancer. Centralising the follow-up care will help healthcare providers gain experience and develop best practice protocols to counsel and treat these patients, in the best interest of the growing cohort of survivors of adolescent and young adult cancers.

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