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Current Perspective

Cancer survivorship: Reproductive health outcomes should be included in standard toxicity assessments

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Abstract It is well established that cancer and its treatment, whether by chemotherapy, radiotherapy, hormone therapy, or surgery, can adversely impact reproductive function in both women and men. The effects of cancer treatment on reproductive function in both sexes may lead to loss of fertility, sexual desire and function, and hormone deficiency, which results in additional long-term morbidity in more than a third of patients. Given the importance of reproductive function to most people, and the often devastating effect of cancer treatment on it, we propose that proactive assessment of the functional and endocrinological impact of treatment be made a vital component of the assessment of modern cancer treatment, and should be a routine part of discussions with patients before and after treatment, both in trials and in routine care. Reproductive counselling should be proactive and encouraged, as implementation of such counselling has been shown to be beneficial to patient mental health, quality of life, and adherence to treatment. Similarly, efforts should be made to provide more adequate and accurate information to patients, as well as to offer appropriate fertility

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preservation approaches, which may potentially influence their treatment decisions.

1. Introduction

There are an estimated 18.1 million new cancer cases worldwide, of which 3.2 million are in those aged up to 49 years [1]. Whilst longitudinal data show that the number of cancer cases in both sexes is increasing [2], 5-year survival rates also continue to improve for many cancers [3]. The issues associated with cancer survivorship are becoming increasingly important to patients [4], and the mindset of clinicians is shifting from keeping the patient alive to optimising quality of life [5]. These long-term toxicities are varied and include cardiovascular toxicity, cognitive dysfunction, loss of sexual function, nephrotoxicity, bone loss, thyroid function loss, and treatment-induced cancers [5]. While some of these are consistently monitored during and after treatment, depending on the known toxicity of the treatment administered, reproductive toxicity is still not sufficiently addressed in routine assessment [6–9]. The provision of 'late effects' clinics is now established in paediatric oncology [10,11], and several countries have guidelines for the surveillance of late effects for affected children [12], but equivalent services for young adults lag behind [13]. We here suggest that reproductive function should be included in routine toxicity assessment in women and men with cancer.

It is well established that cancer and its treatment, whether by chemotherapy, radiotherapy, hormone therapy, or surgery, can adversely impact reproductive function in both women and men [6,14–16]. Chemotherapy and radiotherapy have direct adverse effects on ovarian and testicular function [14], while uterine and vaginal function may both be directly impacted by pelvic radiotherapy [15,17] and endocrine therapy [18,19], or indirectly through disrupted ovarian function [20]. Central hypothalamic pathways may also be impacted by cranial radiotherapy [21], and all components of the reproductive system can be affected by surgery.

The effects of cancer treatment on reproductive function in both sexes leads to loss of fertility, sexual desire, and hormone deficiency. In women, treatment can result in the loss of menstrual cyclicity [22], lower rates of pregnancy and live births [15], vaginal atrophy [18], and early menopause with its many symptoms [15]. Population-based data show that women are 38% less likely to have a pregnancy after cancer, with an impact across all diagnoses [23]. In men, testosterone deficiency results in erectile dysfunction and loss of sexual desire [24]. In addition to the immediate effects in relation to fertility and sexual health, it is increasingly clear that endocrine deficiency has multimorbidity implications for long-term health (bone, cardiovascular, brain) [16,25,26], and indeed reduces life expectancy in both men and women [26,27]. These effects significantly impact on the quality of life (QoL) for survivors and are of central importance to their medical and psychosocial wellbeing [14,28].

2. Long-term adverse effects on fertility

2.1. Women

Chemotherapy can be gonadotoxic and has the potential to impact the ovarian reserve, and thus the fertile lifespan of any premenopausal woman, resulting in premature ovarian insufficiency (POI) [29]. The impacts on fertility, sexuality and reproductive function are among the most important consequences of treatment for young women with cancer [30,31]. In the general population, there is an increasing desire to delay pregnancy past the age of optimal fertility [32]; this, coupled with the adverse effects of cancer therapy, makes young cancer survivors particularly vulnerable to fertility problems. Several studies have shown that, after cancer diagnosis, women aged younger than 40 years still express the desire to have children [33,34]. Female cancer survivors with impacted fertility report significant psychological distress related to reproduction, including depression, feelings of grief, anxiety, anger, and fear [35]. For young women with breast cancer, improved management of fertility and pregnancy-related issues is one of the top three priorities set by patient representatives and patient advocates [36]. Despite this, the assessment of reproductive function and fertility is generally inadequate in the study of the effect of cancer treatments, both during clinical trials and routine practice. The impact of newer molecular targeted agents on fertility (for example, monoclonal antibodies, kinase inhibitors, and immunomodulators) is largely unknown [37,38].

Existing literature suggests that young women are often not adequately counselled regarding their options for future fertility, either prior to starting or during cancer treatment [34,39,40]. While the ability to reliably freeze oocytes, embryos, or ovarian tissue has transformed fertility preservation options, there is considerable variation in how frequently they are used and/or offered to women, reflecting the multiple stakeholders involved in oncofertility service provision and the

associated medical, service organisation and financial considerations [7,39–41]. Optimal long-term treatment of hormone receptor-positive breast cancer in pre- and peri-menopausal women may require up to 10 years' continued ovarian suppression and aromatase inhibition [29], thus effectively abrogating ovarian function, suppressing sexual desire, and making sexual intercourse almost impossible due to vaginal atrophy [18]. Importantly, the experience of adjuvant endocrine therapy-related gynaecological or menopausal symptoms can negatively influence patients' adherence to treatment [42], with a consequent decrease in survival [43,44]. Therefore, careful discussion is required with these patients to weigh up the risk benefits of optimal treatment versus loss of normal sexual and reproductive function.

2.2. Assessment of female reproductive function

The presence or absence of spontaneous menses provides an obvious and important index of ongoing ovarian activity. However, regular cycles may continue in the presence of a very depleted ovarian reserve [45], with likely early onset of POI. Follicle-stimulating hormone (FSH) measurement remains the most established diagnostic test for POI, alongside low oestradiol levels [26]. Women with a reduced ovarian reserve, but ongoing menses, may show an elevated baseline FSH level, but this is often a late event once POI is imminent [46]. A cut-off level of 25 IU/L has been identified to define POI [26], but FSH levels can be quite variable and may only be useful to evaluate fertility at high thresholds [47]; therefore, FSH may be of limited value for fertility counselling.

There is currently much interest in the potential value of the measurement of anti-Müllerian hormone (AMH) in the context of prediction of normal menopause or of loss of ovarian function after cancer treatment [48]. AMH is produced by small growing follicles [49]; their number indirectly reflects the number of remaining primordial follicles, the true ovarian reserve, necessary for ongoing ovarian function [50]. Measuring AMH may help oncologists care for premenopausal women with cancer by allowing precise and unbiased assessment of ovarian reserve at diagnosis, informing decisions for risk-adapted strategies of fertility preservation, providing a method for assessment of ovarian function recovery after chemotherapy or endocrine therapy, and monitoring ovarian reserve in cancer survivors [51–54]. Prospective studies analysing AMH in patients at the time of breast cancer diagnosis and follow-up demonstrated that women who were still menstruating at 2- or 5-year follow-up had higher AMH levels at diagnosis compared with those who developed amenorrhoea [55,56]. This suggests that pre-treatment AMH predicts mid- and long-term ovarian function in early breast cancer. However, there are several critical issues with using AMH as a surrogate marker of gonadal toxicity, such as when and how frequently it should be measured. AMH levels at 2 years after treatment may indicate long-term ovarian function [57], but, potentially, earlier measurements could be useful, and further research is required. In addition, some studies report that the *BRCA1* or *BRCA2* mutation is associated with lower levels of AMH [58,59] and *BRCA2* as being associated with premature ovarian ageing [58], suggesting that the impact of mutation status on reproductive outcomes should be further investigated. Importantly, however, low AMH levels do not predict short-term fertility [60–62], and similarly, there is a poor correlation between AMH level and fertility in cancer survivors who have restored spontaneous menstruation [63]. This remains an active area of research at present, without robust criteria for interpreting low AMH levels (other than a very low/undetectable value in the context of amenorrhoea [63]).

Ultrasound analysis of antral follicle count is also potentially of value, as it can be used as a surrogate marker for the reserve of each ovary separately [64]. However, transvaginal ultrasonography requires specialist skills [64], is generally not available in an oncology setting, and is invasive. Furthermore, due to the lack of standardisation of technique and equipment used, there can often be inconsistencies between observers [64].

2.3. Men

Maintaining fertility in male cancer survivors has a significant impact on QoL [65], with many cancer survivors reporting fertility-related psychological distress [35]. Fertility in patients with testicular cancer, in particular, is important given that cisplatin combination therapy is gonadotoxic, and the malignancy occurs during the peak years of child rearing [66–68]. However, children and adolescents with lymphoma, leukaemia and Ewing sarcomas are also at risk of developing permanent sterility [69]. Leydig cell failure and dysfunction resulting in testosterone deficiency has been observed in survivors of childhood cancer, with the risk increasing with older age, higher doses of testicular radiotherapy, and alkylating agent dose [70].

Fertility preservation techniques include cryopreservation of semen for young adults and men, and spermatogonial stem cells/testicular tissue cryopreservation for prepubertal boys [71]. The latter is still experimental [71], may not be widely available, and to date, no children have been conceived after spermatogonial stem cell or testicular tissue transplant. Despite the concerns regarding the psychological impact of reduced fertility after cancer treatment, the use of sperm banking for young patients with cancer varies. In a systematic review analysing 42 studies from different countries that included patients with various primary tumours and across various ages at diagnosis (13–83 years), the range of patients offered cryopreservation varied from 8 to

100%, the proportion of all at-risk patients attempting cryopreservation varied from 3 to 79%, and the rate of acceptance varied from 13 to 87% [72]. Furthermore, even if sperm cryopreservation was covered by statutory national health insurance, cryopreservation rates may still be low [72], suggesting that removal of financial hurdles alone does not guarantee equal access to fertility preservation, and a range of health inequality barriers remain [8].

2.4. Assessment of male reproductive function

Full assessment of male fertility requires both endocrine and semen analysis, with both requiring specialist laboratory services. Serum luteinising hormone and testosterone measurements can be reliably used to assess testicular Leydig cell function [66]. The importance of ensuring normal testosterone levels is mandated in the event of symptoms of hypogonadism (most importantly sexual dysfunction) [16] and in the long term by epidemiological evidence linking low endogenous testosterone levels to increased risk of all-cause and cardiovascular disease mortality [27]. FSH provides an index of spermatogenesis, with high levels indicating testicular dysfunction [73]. A cut-off level of 10.4 IU/L has been identified through meta-analysis of (albeit limited) data to reliably predict azoospermia in cancer survivors (specificity 81% [95% confidence interval {CI} 76–86]; sensitivity 83% [95% CI 76–89]) [74]. However, confirmation by semen analysis will still be required when conception is desired. A reference range based on standardisation of routine semen analyses (semen volume, sperm concentration, motility, and morphology) in fertile men has been developed and generally adopted by most clinicians working with infertile couples [75], and the lower limit thresholds are used as guidance for determining the next step of diagnosis and treatment, albeit with limitations [76].

2.5. Call to action

Currently, there are several gaps in physician knowledge regarding the impact of cancer therapies on fertility, but routine application of readily available robust biochemical tests and clinical information could be transformative in this field (Table 1).

There is a need for long-term and large-scale follow-up of cancer survivors and the development of evidence-based guidelines to direct surveillance to detect long-term and late effects. In particular, newly emerging classes of systemic therapy, either in routine use or under clinical evaluation in a non-metastatic setting, such as poly-ADP ribose polymerase inhibitors, immunotherapies, or new anti-human epidermal growth factor 2 drugs, have an unknown long-term impact on sexual function and fertility [77–79]. Prospective oncological clinical trials assessing the efficacy of these news drugs in young patients with cancer should be considered as unique opportunities to evaluate their impact on long-term ovarian function within translational research projects. Investigators should be encouraged to routinely measure and report biochemical indices of reproductive endocrinological function. Some clinical trials have only reported adverse events (AEs) above an incidence greater than 15% [80], contributing to misreporting of AEs and limiting the determination of the precise incidence of endocrine AEs, which, whilst they may not be considered by trialists as 'severe', nevertheless may be or may become chronic and consequently have a significant impact on patients, and affect adherence to therapies. Recent statements from societies such as the European Society for Medical Oncology recommend the inclusion of management of anticancer treatment-related toxicities throughout the continuum of the disease course, including survivorship care [81].

Given the importance of reproductive function to most people, and thus to patients with cancer, and the often devastating effect of cancer treatment upon this facet of normal life, we propose that assessment of the impact of treatment on sexual and reproductive function is a vital component of modern cancer treatment, both in trials and routine care. Critically, we call for assessment of gonadal toxicity to be as essential a part of data collection in clinical trials in oncology as toxicities in other organs, and for both male and female patients; without robust and routine collection and proper interpretation of such information, we cannot provide the accurate information to our patients that 'informed consent' and shared decision-making requires. The nature of the information that should be collected to inform such analysis is under debate, but we suggest that both clinical and biochemical indices of reproductive

Table 1
Summary of readily available data that could be recorded to address the impact of cancer therapies on long-term or late adverse effects on reproductive function and the gaps in knowledge.

	Biochemical and clinical data available	What are the gaps in knowledge?
Males	**Biochemical** *FSH* *LH* *Testosterone* *Semen analysis* **Clinical** *Paternity after treatment*	Risks to fertility after different treatment modalities Effect of treatment on adolescent and young adult cancer survivors
Females	**Biochemical** *AMH* *FSH* *Oestradiol* **Clinical** *Menstrual cyclicity* *Pregnancy and pregnancy outcome*	Risks to fertility after different treatment modalities Effect of treatment on adolescent and young adult cancer survivors

AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone.

function should be routinely collected in clinical trials in oncology (Table 1). This is particularly important for new targeted therapies for which there are at present very few data on reproductive toxicity.

The consideration of the need for fertility preservation is already widely considered essential, albeit not always implemented. The impact of treatment should be a routine part of discussions with patients before and after treatment. Fertility counselling should be encouraged, and may require additional skills to be taught to clinical staff: implementation of such counselling has been shown to be beneficial to patient mental health and QoL [35]. Similarly, efforts should be made to provide more adequate and accurate information, and to offer appropriate fertility preservation approaches; this may potentially influence treatment decisions. The timely collection of data on reproductive function associated with a wide range of cancer diagnoses and treatments will greatly inform discussions with our patients and support the development of new treatments and protocols with reduced impact on this function of their lives that patients value so highly.

Conflict of interest statement

D.C. reports no financial competing interests. D.C. reports participating in an advisory board for, and acting as a consultant for, Roche Diagnostics. Both positions involved reimbursement to his employer. FC. reports receiving honoraria from AstraZeneca, BMS, Lilly, Merck and Roche Diagnostics, and his institution receiving research funding from Roche Diagnostics and AstraZeneca. F.P. reports receiving honoraria in the last three years from AstraZeneca, Ipsen and Roche Diagnostics. I.D. reports acting as a consultant for Roche Diagnostics, and receiving speaker honoraria from Novartis. I.D. reports receiving support for congress participation from Ferring and Theramex. M.L. reports acting as a consultant for Novartis, Roche and AstraZeneca, and receiving honoraria from Theramex, Roche, Novartis, Pfizer, Takeda and Lilly. R.A.A. reports acting as a consultant for Roche Diagnostics, IBSA, Merck, Ferring, NeRRE Therapeutics and Sojournix Inc. S.M.N. reports participating in advisory boards and receiving speaker or consultancy fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics and The Fertility Partnership. S.M.N. reports receiving grant funding from government, charity and industry funders, including Roche Diagnostics and Ferring Pharmaceuticals. A.M. reports no competing interests.

CRediT authorship contribution statement

Richard A. Anderson: Conceptualization, Writing - original draft, Writing - review & editing. **Florian Clatot:** Conceptualization, Writing - review & editing. **Isabelle Demeestere:** Conceptualization, Writing - review & editing. **Matteo Lambertini:** Conceptualization, Writing - review & editing. **Adrienne Morgan:** Conceptualization, Writing - review & editing. **Scott M. Nelson:** Conceptualization, Writing - review & editing. **Fedro Peccatori:** Conceptualization, Writing - review & editing. **David Cameron:** Conceptualization, Writing - review & editing.

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