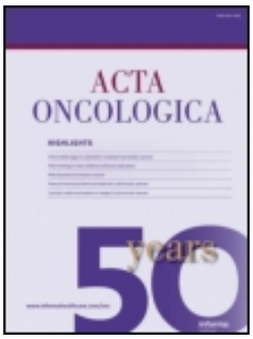

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ORIGINAL ARTICLE

Gonadal dysfunction and fertility problems in cancer survivors

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Abstract

Gonadal dysfunction and fertility problems are adverse effects of cancer treatment or may be associated with specific malignancies. This review focuses on these problems in the young cancer survivors, where methods of protecting or restoring endocrine function and fertility need to be considered. In females, treatment adverse effects can result in infertility, but premature ovarian failure (POF) is probably relevant for more female cancer survivors, affecting also those who do not wish post-treatment parenthood. POF affects present and future health, especially through oestrogen deficiency symptoms and an increased risk of developing osteoporosis. A lower risk of developing POF has been considered in young females than in older due to a larger pool of oocytes. However, a recent long-term follow-up study reported a prevalence of POF in young females with Hodgkin's lymphoma of 37% showing that young age at time of treatment only delays the development of POF. In male gonads, germ cells are much more sensitive to irradiation and chemotherapy than Leydig cells. Thus, infertility is a more common adverse effect than hypogonadism. Some malignancies are particular relevant. Persistent azoospermia was formerly common after treatment for Hodgkin's lymphoma, but currently, most patients recover spermatogenesis. Modern treatment of childhood acute lymphoblastic leukemia is also unlikely to cause infertility. Norwegian testicular cancer survivors diagnosed in 1980–1994 who attempted conception had an overall 15-year actuarial post-treatment paternity rate of 71% (range 48–92% depending on the treatment). However, the rate was significantly higher among men diagnosed in1989–1994 (over 80%) than in 1980–1988 (about 63%). Patients at risk for hypogonadism and infertility should be defined prior to treatment, and available methods for gonadal preservation should maximally be utilised. During follow-up, oncologists should routinely address these issues.

Gonadal dysfunction and impaired fertility are adverse effects of cancer treatment or may be associated with specific malignancies. This review addresses these issues in young cancer survivors where these adverse effects are of special importance. About 7.4% of Norwegian cancer patients are younger than 45 years at diagnosis [1]. Apart from impaired infertility, hypogonadism may lead to distressing deficiency symptoms, including depression and possibly impaired cognitive function [2–4]. Furthermore, there is an increased risk of osteoporosis [5–7] and also concerns regarding cardiovascular diseases [8–10].

Gonadal dysfunction

The gonads have two main roles, the production of sex hormones (testosterone and oestrogens) and germ cells (ova and sperm), which both depend on a normal function of the hypothalamic-pituitary-gonadal axis.

Women have a fixed number of primordial follicles at birth (about 100 000), which are progressively biexpontentially lost during life to about 1 000 at the age of 50 when menopause normally occurs. From birth, the oocytes are in a prolonged resting phase of the first meiotic division, which persists throughout follicular growth before ovulation. Ovarian follicular growth and steroidogenesis depend on a two-cell system within the follicles. Oestrogen production by the follicles is the result of combined luteinising hormone (LH) and follicle-stimulating hormone (FSH) stimulation of Theca and Granulosa cells.

Any insult that reduces the number of follicles leads to an increased risk of premature ovarian

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failure, defined as menopause before the age of 41 years, with decreased production of oestrogens. Decreased oocyte reserve may also result in a lower chance of subsequent conception, despite maintenance of menstrual cycles [11]. Depending on the remaining number of oocytes, the ovarian function may cease immediately, or may, sometimes after transient amenorrhea, function normally for a period of time before the injury can become manifest through premature ovarian failure [12].

In men, the production of mature sperm cells starts around the age of 12–14 (spermarche) after which new spermatozoa continuously are produced from the stem cells (spermatogonia) of the germinal epithelium, a process that takes approximately 70 days. The Leydig cells produce testosterone in response to LH, and testosterone together with FSH stimulate the Sertoli cells, which provide physical and nutritional support for spermatogenesis [13]. The germinal epithelium has a high mitotic rate and is more sensitive to radiation and cytotoxic treatment than the testosterone producing Leydig cells [14,15].

Fertility

Impaired fertility may result from gonadal dysfunction as well as injury of the other reproductive organs or, in males, the nerves responsible for semen emission and ejaculation. In addition, some malignancies are associated with reduced male fertility, even prior to treatment.

Testicular cancer is a malignancy where there is evidence of a shared aetiology, as both testicular cancer and subfertility together with cryptorchism and hypospadias are parts of the Testicular Dysgenesis Syndrome [16]. The median sperm count prior to treatment in men with testicular cancer is only about 1/3 of that of the general male population [17], and biopsies have revealed probably irreversibly impaired spermatogenesis in the contralateral testicle in 24% of patients [18].

Hodgkin's lymphoma is also associated with male subfertility prior to treatment, with up to 34–44% of patients having azoospermia or oligospermia, [19,20] and overall impaired spermatogenesis in about 1/2–2/3 of patients [19–21]. The pathogenesis is not clearly understood, but it has been hypothesised that it might be immune-mediated and several cytokines have attracted interest [19,22]. This hypothesis implies that although dyspermia can be present at diagnosis, it seems potentially reversible after cure by non-gonadotoxic treatment [22]. As to the association with clinical features, Rueffer et al. found an association with high ESR and advanced stage, but not systemic symptoms [19]. Others found neither stage nor B-symptoms to be significant factors [20,21].

Overall, age at the diagnosis of the malignancy (15–30 years vs. 30–45 years) and gender are strongly associated with the post-treatment probability to become parents, however with large variability between the cancer types (Figure 1) [23].

The effects of cancer treatment on fertility and gonadal function

Surgery

Any surgery involving the gonads or reproductive organs may impair fertility. Uterine cervical cancer and ovarian cancer are the most common gynaecological cancers during reproductive age, and infertility is in most cases inevitable as the organs are removed. However, in women with early-stage cervical cancer who want to preserve fertility, trachelectomy (resection of the cervix) is an option. Sheperd et al. reported a cumulative conception rate of 53% following this procedure, but the premature labour and miscarriage rate was relatively high, with 28 live births in 55 pregnancies [24]. Conservative surgery with unilateral adnexectomy may be considered in young patients with good prognostic borderline tumours of the ovary who wish to preserve fertility [25].

Decreased sperm concentration is seen in most men after unilateral orchiectomy for testicular cancer [26], but there is some recovery after one year [27]. Of clinical importance is especially that post-orchiectomy azoospermia may occur in men who are highly oligospermic prior to orchiectomy [26].

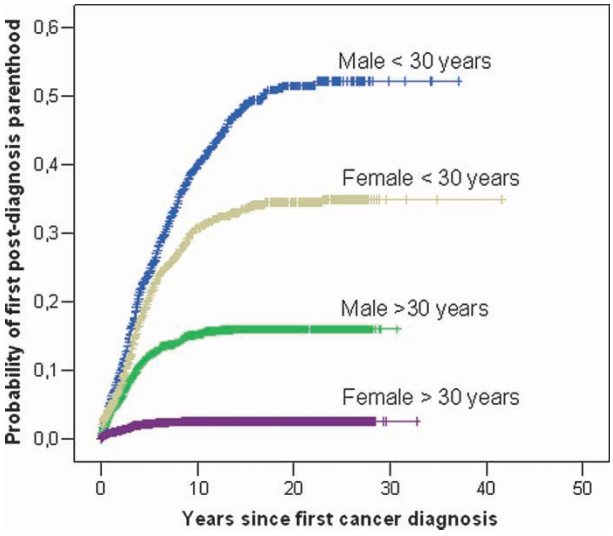

Figure 1. Probability of first post-diagnosis parenthood according to age and gender in cancer patients aged 15–45 at diagnosis. Reprinted (modified) with permission from reference [23]© (2005) Oxford University Press.

Therefore, semen cryopreservation should preferably be offered before unilateral orchiectomy.

Retroperitoneal surgery may injure the postganglionic nerves of the hypogastric plexus which are involved in semen emission and ejaculation. In the late 70s and early 80s, loss of antegrade ejaculation occurred in about 90% of testicular cancer patients undergoing retroperitoneal lymph node dissection [28,29]. The incidence of this complication was dramatically reduced through subsequent modifications of surgical techniques, and today, nerve-sparing RPLND preserves ejaculatory function in virtually all patients with low-stage disease [28]. After induction chemotherapy for metastatic disease, Jacobsen et al. reported preserved ejaculation function in 89% following nerve-sparing RPLND [29].

Radiotherapy

Gonadal dysfunction following radiotherapy may occur when the gonads are close to or within the radiation field. The testis represents one of the most radiosensitive tissues, and the effects of single doses in healthy males' testicles are documented by Rowley et al. [14]. The testes are, however, even more sensitive to fractionated treatment where temporary azoospermia among testicular cancer patients has been reported following 0.2–0.6 Gy [30]. In 17 Hodgkin's lymphoma patients, Kinsella et al. reported no significant effect on FSH levels or sperm counts at doses below 0.2 Gy, but transient dose dependent changes between 0.2 and 0.7 Gy which all returned to normal within 12–24 months [31].

Spermatogenesis is generally restored after 1–2 years, but recovery may be incomplete or take several years in some patients, also depending on the dose and the patient's age [30]. There is no well defined threshold where permanent azoospermia is inevitable, but prolonged azoospermia should be expected at 2.5 Gy total dose [11]. Some studies suggest lower thresholds, although longer follow-up might lead to further recovery. Among seven men with Hodgkin's lymphoma who had normal sperm counts prior to treatment with testicular doses of 1.4–2.6 Gy, all had azoospermia at last follow-up (17 months in one, 29–47 months in the remaining six) [32].

After dog-leg /hockey stick field radiation in testicular cancer patients, the mean testicular dose is reported to be 0.32–0.55 Gy, compared to 0.09–0.25 Gy when irradiation is limited to the paraaortic nodes [33,34]. In the last case, no or minimal changes are seen in FSH and sperm concentrations 6–12 months after radiotherapy [33,34].

The testosterone-producing Leydig cells are less radiosensitive, and the biochemical abnormalities are usually mild with raised LH levels with normal of low testosterone levels. Significant rises in LH have been demonstrated after irradiation >2 Gy total dose of fractionated treatment with a gradual return within 30 months [35]. Among 42 men with one remaining testicle treated with 14–20 Gy for carcinoma in situ of the testis, 18 (43%) needed androgen substitution therapy [36]. Dueland et al. found a 25% fall in s-testosterone 4–6 weeks after a pelvine dose of 45–60 Gy for rectal cancer, with measured testicular doses of 3.7–13.7 Gy [37]. Others have found similar fall in testosterone, and these patients should be informed about the risk of endocrine failure and the high risk of permanent infertility [38].

In females, only a few cells in each ovarian cycle are in meiotic activity, and the ovaries are hence less sensitive to radiation than the testes. However, due to their location within the pelvis, the ovaries more often receive higher doses. Ovarian impairment is related to the biologic dose of radiotherapy as well as the age at treatment, or more precisely, to the number of remaining follicles. The ED50 for oocytes is below 2 Gy and the predicted age for ovarian failure at given age and dose can be calculated or looked up in tables [39].

Oophoropexy, surgical transpositioning the ovaries outside the radiation field, may reduce the radiation dose, but due to altered ovarian blood flow, scattered irradiation and also subsequent remigration of the ovaries, the success rate (measured as short term preserved menstrual function) is about 50% [11]. The gonads may also partly be protected during radiotherapy by gonadal shielding, but the distance from the field border and the positioning of the testes are also important [33]. Testicular shielding is commonly applied in men with lymphoma or testicular cancer, but should be considered in other diagnoses involving abdominopelvic radiotherapy as well [40].

The prospects of pregnancy following radiation damage to the uterus are best studied after treatment for childhood cancer, and there is an increased risk of miscarriage, preterm labour and low birth weight babies [41].

Total body irradiation as part of the conditioning regime before bone marrow transplant is associated with a high incidence of infertility and POF [42]. Fertility and endocrinological disturbances including both early and delayed puberty may occur following cranial radiation [43].

In most patients treated with ^{131}I for thyroid cancer, treatment induced compromised fertility is not a concern [44,45]. However, sperm banking

should be considered if multiple administrations are likely as cumulative doses above 14 GBq might be associated with impaired spermatogenesis [44].

Chemotherapy

The gonadal effects of chemotherapy depend on type of drug, cumulative doses, the combinations used, the age and the pretreatment gonadal status of the patient. The alkylating drugs and procarbazine are the most gonadotoxic cytostatics (Table I) [11,12,46]. A recent publication from the American Society of Clinical Oncology summarises the effects on sperm production and risks for permanent amenorrhea according to various treatment regimes or dose of cytostatics [11]. There are little systematically achieved data for newer drugs such as taxanes, oxaliplatin, irinotecan, monoclonal antibodies and tyrosine kinase inhibitors.

The MOPP regime (mustine, vincristine, procarbazine and prednisolone), which was previously commonly used in the treatment of Hodgkin's lymphoma, leads to permanent sterility in the majority of male patients, and to premature ovarian failure and also infertility in females. In a study by Viviani, azoospermia was induced in 97% (28/29) of patients, and recovery was seen in only 14% (3/21) of those who were tested after 18–58 months [47]. After treatment with the ABVD regime (doxorubicin, bleomycin, vinblastin and dacarbazine) which is commonly used today, azo- or oligospermia was induced in 54% (13/24) of patients. Moreover, full recovery was seen in all 13 who were retested.

Pryzant et al. reported on 71 non Hodgkin lymphoma patients, treated with CHOP-based chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone), some in combinations with RT or other cytostatics [48]. All had azoospermia during treatment, but 67% recovered to normospermia (defined as 10 x 10^6/ml) within 5 years, with further 5% being oligospermic. Recovery was however dependent on cumulative dose, with 83% recovering at cyclophosphamide doses <9.5 g/m2, 47% >9.5 g and only 20% of those who also received pelvic RT recovered.

Modern treatment of childhood Acute lymphoblastic leukaemia (ALL) is unlikely to cause infertility, but long-term follow-up is needed to be certain [15]. Byrne et al. studied proven fertility (ever pregnant or pregnant partner) in a cohort of ALL survivors (average age 23 years) treated between 1970 and 1987 compared to sibling controls. The proven fertility in male survivors was not significantly impaired, apart from those treated with cranial radiotherapy at young age [49]. The female survivors had a fertility deficit, most pronounced for those treated with cranial radiotherapy around menarche [50].

Based on sperm analyses in 178 testicular cancer patients, Lampe et al. defined risk groups for recovery of spermatogenesis according to pretreatment sperm counts, number of cycles and carboplatin versus cisplatin based regimes [51]. If not azoospermic prior to treatment, there was a medium chance (defined as 65% at 3 years and 80% at 4 years) of recovery to at least oligospermia after up to four cisplatin based cycles. After more than four cycles, the chance of recovery was less (25% in 3 years and 45% at 5 years).

Brydøy et al. have analysed paternity among 554 testicular cancer survivors who had tried to conceive after treatment, and found an overall 15 year actuarial paternity rate of 71% [52]. This rate was 92% in those who were on surveillance following orchiectomy, 64% in those who were treated with total cumulative cisplatin doses up to 850 mg (corresponding to four or less cycles), some in combination with radiotherapy or retroperitoneal surgery, and 48% in those who were most intensively treated, with cisplatin doses exceeding 850 mg (more than 4 cycles) (Figure 2). However, the rate was significantly higher among men diagnosed in1989–1994 (over 80%) than in 1980–1988 (about 63%). Others have reported conception rates of

Table I. Risk of gonadal dysfunction according to cytotoxic drugs [11,12,46].

High risk	Medium risk	Low risk	Limited data
Alkylating drugs	Platinum analougs	Plant derivatives	Taxanes
Cyclophosphamide	Cisplatin	Vincristine	Oxaliplatin
Ifosfamide	Carboplatin	Vinblastine	Irinotecan
Busulfan	Doxorubicin	Antibiotics	Tyrosine kinase inhibitors
Melphalan		Bleomycin	Monoclonal antibodies
Chlorambucil		Dactinomycin	
Chlormethine		Antimetabolites	
Procarbazine		Methotrexate	
		Mercaptopurine	
		5-fluoruracil	

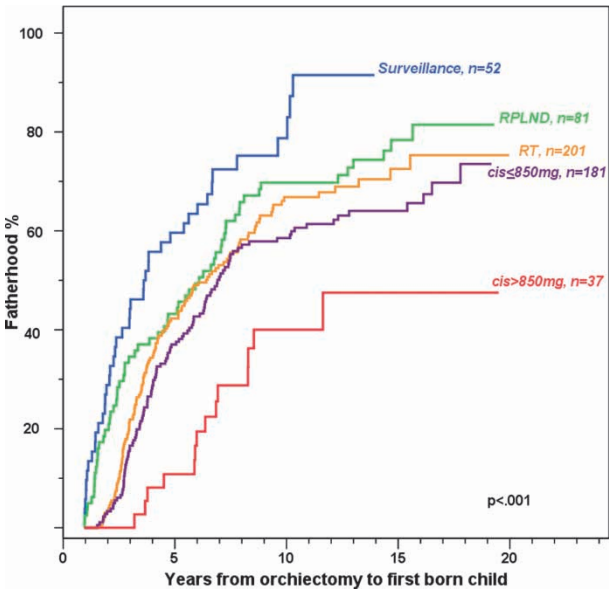

Figure 2. Actuarial post-treatment paternity rates according to treatment in 554 testicular cancer survivors who attempted post-treatment conception without the use of cryopreserved semen. RPLND = retroperitoneal lymph node dissection; RT = radiotherapy; cis = cumulative cisplatin dose. Reprinted (modified) with permission from reference [52] © (2005) Oxford University Press.

75–85% following chemotherapy for testicular cancer [53,54].

Nord et al. evaluated Leydig cell function among 1 235 testicular cancer survivors compared to a control group [55]. Mean s-testosterone was similar in cases and controls, but there was a marked difference in the occurrence of hypogonadism, with an overall odds ratio of 3.8 compared to controls (Table II).

In women, permanent amenorrhea is often considered as a measure of gonadotoxicity, while detailed data on the risk of a later occurring premature

Table II. Age adjusted odds ratios for hypogonadism (defined as s-testosterone below 8 nmol/l, using testosterone supplementation or a value of serum luteinizing hormone >12 IU/l) in long term testicular cancer survivors compared to controls. Reprinted (modified) with permission from reference [55] © (2003) European Association of Urology.

	Hypogonadism	Adjusted odds ratios (95% CI)
Controls	5%	1.0
Testicular Cancer Survivors	16%	3.8 (2.0–7.3)
Treatment		
Controls	5%	1.0
Surgery	9%	2.0 (0.9–4.2)
Radiotherapy	16%	3.5 (1.8–7.0)
Cisplatin ≤850 mg	19%	4.8 (2.4–9.5)
Cisplatin >850 mg	27%	7.9 (3.6–17.4)

Table III. Prevalence of POF among women treated for Hodgkin's lymphoma (HL) according to age, stage and chemotherapy given. Reprinted with permission from reference [57] © (2006) Oxford University Press.

	Number with POF/total (%)	p
Age at diagnosis HL		1.00
9–29 years	23/62 (37%)	
30–40 years	14/37 (38%)	
Stage at diagnosis HL		0.03
Stage I and II	20/67 (30%)	
Stage III and IV	17/32 (53%)	
Chemotherapy		<0.001
No	4/32 (13%)	
Yes, all	33/67 (49%)	
Yes, without alkylating agents[a]	3/13 (23%)	
Yes, including alkylating agents[b]	30/54 (56%)	

[a]Epirubicine, bleomycin, vinblastine, prednisone (EBVP) or adriamycin, bleomycin, vincristine, dacarbazine (ABOD).
[b]Mustine, vinblastine, procarbazine, prednisone (MVPP) or chlorambucil, vinblastine, procarbazine, prednisone (ChlVPP).

ovarian failure or compromised fertility due to decreased ovarian reserve is sparser. After ABVD or 4–6 cycles of CHOP the risk of permanent amenorrhea has been reported to be below 20% [11]. A recent study found similar time to pregnancy and 12 months pregnancy rates in female Hodgkin lymphoma survivors and controls [56]. The gonadal effects of adjuvant treatment with 6 cycles of FEC (5-fluorouracil, epirubicin and cyclophosfamide) for breast cancer are dependent on age, with a high (above 80%) risk of permanent amenorrhea in women above 40 years, a medium risk for women in their 30's, and low (<20%) for women in their 20's [11].

Recently, Haukvik et al. published long-term results on premature ovarian failure in Hodgkin's lymphoma patients with at least 10 years follow-up [57]. All patients received radiotherapy (not infradiaphragmatic), with or without chemotherapy. They found a 15 year cumulative risk of post-treatment premature ovarian failure (POF) of 37% (Table III), and concluded that the risk of treatment related POF is higher than earlier estimated. They also found that the life-time risk was independent of age at treatment as young age only delayed the development of POF. Alkylating agents also increased the risk compared to cytostatic regimes without alkylating agents [57]. They also reported that as many as 26% of the patients with POF had never used hormone therapy, and some had started such treatment several years after their last menstruation.

Preservation of fertility and gonadal function

Patients at risk for hypogonadism and infertility should be defined prior to treatment, and these issues should be discussed with the patient. Preservation options for gonadal function, especially in females, depend on the patient's age, diagnosis, type of treatment, time available, whether the patient has a partner and the national legislation. There are also ethical considerations.

Established methods

Organ-sparing surgery in borderline ovarian tumours, choosing protocols with the least gonadotoxic drug when possible, and optimal gonadal shielding during radiotherapy, may potentially preserve both sex-hormone production and fertility. Organ sparing surgery for small testicular tumours may be considered for preservation of testosterone production in individualised cases, but subsequent radiotherapy leads to infertility [58]. Postponement of postoperative testicular radiotherapy can be considered to allow repeated sampling of semen for cryopreservation or natural conception.

The only other established fertility sparing methods are sperm and embryo cryopreservation [11,12]. Sperm cryopreservation is an easy and rather cheap procedure with little preparations, and should be considered in all males above the age of 12–13 (spermarche) who are scheduled for potentially gonadotoxic treatment, even when the chances for permanent infertility may be low. This should be done prior to initiation of cancer treatment, ideally also before orchiectomy in testicular cancer patients [26]. If retrieval of sperm by masturbation fails, which especially may be the case in young adolescents; other methods for sperm retrieval may be considered, like electroejaculation, electrovibration, microsurgical epididymal aspiration or testicular sperm cell extraction (TESE) [59,60]. The last two procedures may even reveal sperm in men with non-obstructive azoospermia, although the pregnancy rate following ICSI is lower in cases of non-obstructive than obstructive azoospermia [60].

Embryo cryopreservation requires a partner, and is also limited by the need of hormonal stimulation, which has to start at the beginning of the menstrual cycle, and consequently, cancer treatment must be postponed for 2–6 weeks [11]. For women with hormone responsive tumours, there are special concerns both to the stimulation and to later pregnancy. Tamoxifen or aromatase inhibitors in combination with gonadotrophin treatment have been studied as alternatives with reduced oestrogen exposure for stimulation in these patients [61].

Experimental methods

Experimental methods are the only options in prepubertal boys and girls, as well as females who do not have a partner.

Cryopreservation of unfertilised oocytes and ovarian cortical strips or biopsies is still regarded as experimental, as these are more vulnerable for cryopreservation than embryos [62]. Freezing of ovarian tissue (cortical strips or biopsies) does not require hormone stimulation and do not delay cancer treatment more than what is required to do the procedure. Resumption of endocrine function and live birth has been described after transplantation of frozen-banked ovarian tissue [62].

Cryopreservation of testicular tissue or spermatogonial stem cells harvested from biopsies involves the challenge of how to mature the diploid spermatogonia to haploid mature sperms. Hopes for future research are that spermatogonial stem cells can be re-implanted after cancer treatment and recolonise the seminepherous tubuli and restore 'natural fertility', or mature sperm cells can be retrieved by autografted or xenografted testicular tissue, or by in vitro maturation of stem cells [63]. The two latter approaches circumvent the possibility of reintroducing malignant cells in cases where the testicular tissue contained cancer cells at the time of collection. In addition to the scientific and technical issues that have to be solved, there are also ethical and legal issues that must be addressed [63].

Hormonal suppression of the gonads during cancer treatment is still a subject of research. Blumenfeld et al. reported already in 1996 that ovarian suppression with gonadotrophin-releasing agonists may reduce the prevalence of POF in young lymphoma patients treated with chemotherapy [64]. A protective effect of oral contraceptives during chemotherapy has also been suggested [65]. However, hormonal suppression of the ovaries are controversial, and large randomised clinical studies should be performed [11]. In male cancer patients, gonadotrophin-relasing hormone analogues have not proven effective in the clinical situation, despite promising results in rodents [66]. However, further studies have been encouraged [66].

Monitoring gonadal function and management of post-treatment hypogonadism and infertility in the oncological daily practice

During follow-up of cancer survivors at risk of gonadal dysfunction and/or infertility, the patients should routinely be asked for symptoms typical for hypogonadism [3,4] and infertility problems.

Signs consistent with hypogonadism should be looked for. Routine laboratory tests easily performed in oncological practice are shown in Table IV. Patients should be referred to other specialists (endocrinologists, gynaecologists, andrologists) for further evaluation when indicated. The determination of LH and FSH helps to differentiate between hypergonadotrophic (i.e primary gonadal) or hypogonadotrophic (secondary to a disorder at the hypothalamic or pituitary level) gonadal failure [13].

Substitution therapy with androgens or oestrogens should be considered. For men, there is no defined testosterone value where substitution therapy should be initiated. The biologically active or free testosterone value can be calculated through an internet based calculator (http://www.issam.ch/freetesto.htm). For this calculation, sex hormone binding globuline (SHBG) and preferably also albumin has to be measured (if not available, a standard of 4.3 g/dl or 43 g/l can be used for albumin).

Data from prospective clinical trials on women with POF are lacking and there are many unanswered questions regarding substitution therapy in this group [67]. The known risks of hormone therapy in women following normal menopause who prolong their exposure to oestrogens may not be applicable for younger women with POF who restore a natural oestrogen level for their age. In general, women with POF should be treated with hormone replacement therapy [67]. However, there are special concerns regarding survivors of hormone responsive cancers.

With the last decades advances in assisted reproductive techniques, many cancer survivors are now able to have biological children, despite compromised fertility if these issues are considered before treatment and during follow-up. We will just address a couple of points in this review.

Table IV. Laboratory based monitoring of gonadal function in oncological practice.

	Female	Male
s-Luteinising Hormone	Early follicular phase (day 1–3)	Independent of time
s-Follicle stimulating Hormone	Early follicular phase (day 1–3)	Independent of time
s-Oestradiol	Early follicular phase (day 1–3)	Not necessary
s-Testosterone	Not necessary	Early morning due to diurnal variations
s-SHBG	Not necessary	To estimate free and bioavailable testosterone
s-Progesterone	Late follicular phase (day 21–23)*	Not relevant
Sperm analysis	Not relevant	Should be repeated with at least 2 weeks interval

*To verify if ovulation has taken place.

In case of retrograde ejaculation, medical treatment with sympaticomimetica or other drugs may restore antegrade ejaculation and allow natural conception in some couples and is a natural first choice [68]. If medical treatment fails, there are also other available methods for retrieval of sperms [59,60]. Testicular sperm cell extraction is also an opportunity in men with non-obstructive azoospermia following chemotherapy, and in one study, sperm were in such cases extracted in 70% (14/20), and parenthood was achieved by 8 of 12 couples where intracytoplasmatic sperm cell injection (ICSI) subsequently was performed (including one ongoing pregnancy at the end of the study period) [69].

Progeny

Studies so far have not proved any increase of the rate of congenital malformations or genetic diseases in the offspring of cancer survivors, mostly conceived by natural conception [23,70]. However, assisted reproductive techniques like ICSI may bypass some of the selection mechanisms naturally involved in fertilization. There is no evidence that children conceived by this method in the general population have an increased proportion of malformations [63].

Based on available data, couples are advised to use contraceptives and avoid conception during and for some time after cancer treatment [71,72]. Advising on the duration of contraceptive use after cancer therapy is influenced by many factors, but in general, we recommend at least one year, preferably 18–24 months. Although observable effects in offsprings of radiation exposed human populations have so far not been demonstrated [72], and the studies on offsprings of cancer survivors are reassuring [23,70], experimental animal data indicate that mutagenic effects can be seen in offspring from matings that take place during or immediately after treatment of the male with chemotherapy or radiation [71]. Overviews of available human data on chemotherapy administered during pregnancy conclude that timing (first trimester) as well as the chemotherapeutic agent used affect the risk of miscarriage and congenital abnormalities [73]. Compared to controls, increased frequency of sperm aneuploidy has been seen in testicular cancer patients studied 6–18 months after treatment with cisplatin, etoposide and bleomycin [74].

Conclusions

Cancer treatment involves the risk of compromised fertility and insufficient sex hormone production with secondary consequences for a cancer survivor's health. These issues should be discussed with the patient prior to the initiation of cancer treatment and available methods for gonadal preservation should maximally be utilised. During follow-up of cancer patients after treatment, oncologists have to be aware of gonadal dysfunction. Some, though not all, endocrinological deficits and infertility problems can be reduced by interdisciplinary co-operation between oncologists, gynaecologists and endocrinologists/andrologists.

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