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Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer 2

Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Male patients with childhood, adolescent, and young adult cancer are at an increased risk for infertility if their treatment adversely affects reproductive organ function. Future fertility is a primary concern of patients and their families. Variations in clinical practice are barriers to the timely implementation of interventions that preserve fertility. As part of the PanCareLIFE Consortium, in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group, we reviewed the current literature and developed a clinical practice guideline for fertility preservation in male patients who are diagnosed with childhood, adolescent, and young adult cancer at age 25 years or younger, including guidance on risk assessment and available methods for fertility preservation. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to grade the available evidence and to form the recommendations. Recognising the need for global consensus, this clinical practice guideline used existing evidence and international expertise to rigorously develop transparent recommendations that are easy to use to facilitate the care of male patients with childhood, adolescent, and young adult cancer who are at high risk of fertility impairment and to enhance their quality of life.

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This is the second in a **Series** of three papers about fertility preservation in childhood, adolescent, and young adult cancer

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Introduction

Advances in treatment for childhood, adolescent, and young adult (CAYA) cancer (ie, diagnosed aged ≤25 years) have produced 5-year survival rates that exceed 80% in Europe and in the USA.[1,2] This progress has focused attention on reducing the late effects of treatment and optimising future quality of life for the growing population of survivors of CAYA cancer. Male patients with CAYA cancer are at increased risk for hypogonadism and infertility if treatment includes gonadotoxic chemotherapy or radiotherapy to volumes exposing the testes or hypothalamic–pituitary axis, or if abdominal surgery has adversely affected the function of reproductive organs.[3–5] Impaired spermatogenesis and secondary sequelae of androgen deficiency can result in infertility or reduced fertility.[6,7] Newly diagnosed male patients with CAYA cancer, survivors of CAYA cancer, and their parents highly value biological children,[8] and, for them, fertility is a substantial concern later in life.[9,10]

Studies indicate that patients with CAYA cancer are not always adequately counselled about the adverse effects of cancer treatment on reproductive function and options for fertility preservation.[11–13] Patients with CAYA cancer and their health-care providers need accurate, evidence-based clinical practice guidelines (CPGs) that provide a personalised infertility risk assessment and guidance on options for preserving fertility to facilitate informed decision making. A previous report showed that existing CPGs for fertility preservation that were developed by different groups and institutions vary extensively and only about one-third are derived from rigorous methodology.[14] To facilitate global consensus on this topic, we present a systematic review and recommendations for fertility preservation in male patients who are diagnosed with CAYA cancer. These recommendations have been proposed by the EU-funded research project PanCareLIFE[15] in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).[16]

Data collection

Guideline panel formation

A multidisciplinary panel of 31 international specialists in paediatric oncology and haematology, radiation oncology, endocrinology (including paediatric endocrinology), reproductive medicine, urology, andrology, psychology, epidemiology, and guideline methodology was convened (appendix pp 1–2). Members of the expert panels were selected (by MMH, LBK, MDvdW, LCMK, JLe, and WJET) because of their experience, publications,

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and knowledge in the fields of paediatric and reproductive medicine. An overview of the process and structure of guideline development is presented in the appendix (pp 3–4).

Scope and definitions

The aim of this CPG is to help health-care providers to communicate the potential risks for hypogonadism (ie, impaired spermatogenesis, testosterone deficiency, and central hypogonadism) and infertility and the options for fertility preservation to male patients who are diagnosed with childhood cancer tumour types aged 25 years or younger and to their parents, caregivers, or partners (hereafter referred to as families). Additionally, the aim is to provide guidance about how and when to offer methods for fertility preservation. This effort distinguishes between prepubertal and pubertal or postpubertal patients at the time of counselling. The onset of puberty was defined as Tanner Stage II (corresponding with testicular volume of ≥4 cm^3).[17] The guideline panel defined impaired spermatogenesis and testosterone deficiency as outcomes that might lead to infertility.[5,6] Central hypogonadism as a consequence of cranial radiotherapy can result in secondary infertility. Although gonadal function is not affected, testicular function can be impaired by damage to the hypothalamic–pituitary axis. In this case, hormone therapy can restore gonadal function, thus the panel agreed that patients who will be treated with cranial radiotherapy should be considered to be a separate group in this guideline. The standard definitions of gonadotoxic treatment methods and outcomes are presented in the appendix (p 5).

Systematic literature review

The experts formulated clinical questions covering the following key issues: who should be informed about potential infertility risk; who should be counselled about fertility preservation; and what reproductive preservation methods are appropriate to offer in counselling of prepubertal and postpubertal male patients with CAYA cancer (appendix pp 6–8). Formulation of clinical questions was based on discordant areas among recommendations that were identified in existing CPGs for fertility preservation in patients with CAYA cancer, as described by Font-Gonzalez and colleagues,[14] and on controversial issues that were identified within the guideline panel from discussions between panel members. Full details on the search strategies and inclusion criteria that were used to answer each clinical question are provided in the appendix (pp 9–14).

Search strategy and selection criteria

We updated the previous recommendations from the IGHG regarding who should be informed about potential infertility risk.[5] For the other questions, additional systematic literature searches were done in collaboration with Cochrane Childhood Cancer. We searched MEDLINE (through PubMed) for literature that was published between Jan 1, 1993, and Feb 21, 2020, using different combinations of the search terms "childhood cancer", "male", "chemotherapy", "radiotherapy", "orchiectomy", "impaired spermatogenesis", "testosterone deficiency", "semen analysis", and "fertility preservation". Only reports that were published in English were reviewed. Eligible study populations for the risk assessment working group were male patients with cancer, of which 75% or more had been diagnosed with cancer at age 25 years or younger, and at least 50% or more had been followed up for more than 2 years after cancer diagnosis. All study designs were eligible if they controlled for important confounding factors (eg, cancer treatment, age, and follow-up duration) and their sample sizes were above 20 patients. We did not apply a restriction on sample size when assessing novel agents (eg, tyrosine-kinase inhibitors, demethylating agents, and oxaliplatin). Eligible study outcomes were impaired spermatogenesis, testosterone deficiency, ejaculation disorders, obstructive azoospermia, central hypogonadism, livebirths, and fathering a pregnancy. For the fertility preservation methods working group, eligible study populations included 75% or more male patients who were diagnosed with CAYA cancer. Eligible outcomes included livebirths, fathering a pregnancy, quality and yield of sperm, and complications of the method for fertility preservation that were related to the patients and to the offspring.

Furthermore, due to the scarcity of data that were available on methods for fertility preservation, additional evidence that was cited in existing high-quality evidence-based guidelines for fertility preservation, identified by Font-Gonzalez and colleagues,[14] was included without restriction to cancer diagnosis at age 25 years or younger (hereafter referred to as existing guidelines).[18–25] We consulted experts to establish whether additional evidence was missing, and we crosschecked references of relevant literature reviews and reports identified in our searches.

Selection of studies was independently done by the primary reviewers (AF-G, RLM, and EAHL) and cross-checked by the 18 expert panel members. Detailed information from each eligible study was extracted into evidence tables and collated in summary of findings tables. The quality of the evidence was appraised by use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[26]

Recommendations

GRADE Evidence to Decision frameworks were used to formulate recommendations in a systematic and transparent manner.[27] For each method of fertility preservation, the balance between potential benefits and harms was established. The strength of the recommendations was graded according to published evidence-based methods (appendix p 15).[28,29] Final recommendations were based on scientific knowledge combined with other considerations, including clinical judgment, costs, ethical

issues, and the need to maintain flexibility across health-care systems. The recommendations were critically appraised by two independent external experts in the field (Adam Glaser and Zoltan Antal; appendix p 2) and one patient or survivor representative (JdH). All experts and the survivor agreed with the formulated recommendations. Wording of some of the recommendations was refined, but the main message was not changed. Any discordance was resolved by a discussion until agreement was found. After external review, the total guideline panel reviewed the recommendations and manuscript.

Findings

Of 2932 articles identified, 546 were subjected to a full-text review and 30 were eligible for inclusion, including the evidence described in the previous IGHG publication[5] (figure 1). The tables containing conclusions of evidence and the Evidence to Decision frameworks are presented in the appendix (pp 18–37). The recommendations are presented in figure 2 and the appendix (pp 38–42). We present the evidence and recommendations for the three key issues described.

Who should be informed about potential infertility risk?

Evidence concerning desire for and satisfaction with information

Regarding evidence of desire for and satisfaction with information, low-quality evidence showed that not all male patients with cancer and their families were satisfied with the completeness of the information about fertility preservation that was provided.[13] Moreover, low-quality evidence showed that postpubertal patients with cancer strongly desire information about the effects of cancer treatment on fertility and their options for fertility preservation.[30] Similarly, we identified one in-depth interview study in a research setting that reported that most parents of prepubertal boys desired information on testicular biopsy irrespective of infertility risk before initiation of therapy (low-quality evidence).[31] Paediatric oncologists also reported that patients and their parents desire information about fertility preservation but have difficulties initiating discussions on this topic (very low-quality evidence).[32]

Recommendations

The panel agreed that all patients with cancer and their families have the right to be informed about their potential risk for infertility. Therefore, we strongly recommend that health-care providers inform all patients and their families about the expected risk of infertility, which can vary in magnitude on the basis of the specific treatment that is planned (very low-quality to low-quality evidence).

Who should be counselled about fertility preservation?

Evidence concerning risk groups

Based on previously published IGHG data and newly identified data, there is high-quality evidence that alkylating agents are associated with a dose-related (ie, higher cyclophosphamide-equivalent dose) increased risk of impaired spermatogenesis in survivors of CAYA cancer.[5,33,34] Low-quality evidence was found for an increased risk of testosterone deficiency in survivors of CAYA cancer who were treated with increasing doses of alkylating agents.[5,33,35]

Regarding the risk for specific alkylating agents, the risk of impaired spermatogenesis increases with increasing doses of cyclophosphamide (high-quality evidence)[5,33,34] and with increasing doses of procarbazine and chlormethine (given as part of multi-agent treatment) compared with not receiving procarbazine and chlormethine (very low-quality evidence).[5] Low-quality evidence was identified for a decreased likelihood of fathering a pregnancy after increasing doses of cyclophosphamide, ifosfamide (>50 g/m²), and procarbazine in survivors of CAYA cancer.[3,36]

No studies examined the risk of impaired spermatogenesis after antimetabolites. Treatment with antimetabolites showed no significant association with reduced testosterone concentration (low-quality evidence).[5] Additionally, one study reported that survivors who received cytarabine were not less likely to sire a pregnancy than were survivors who did not receive cytarabine (low-quality evidence).[3]

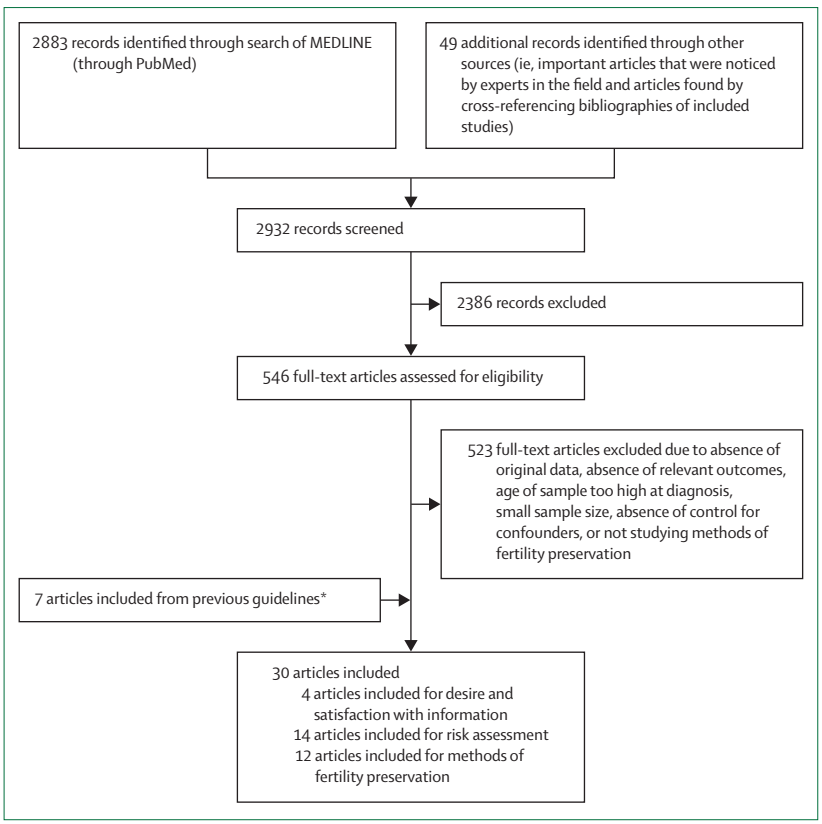

Figure 1: **Flow diagram for selection of studies**

*International Late Effects of Childhood Cancer Guideline Harmonization Group clinical practice guideline for surveillance of male gonadotoxicity.[5]

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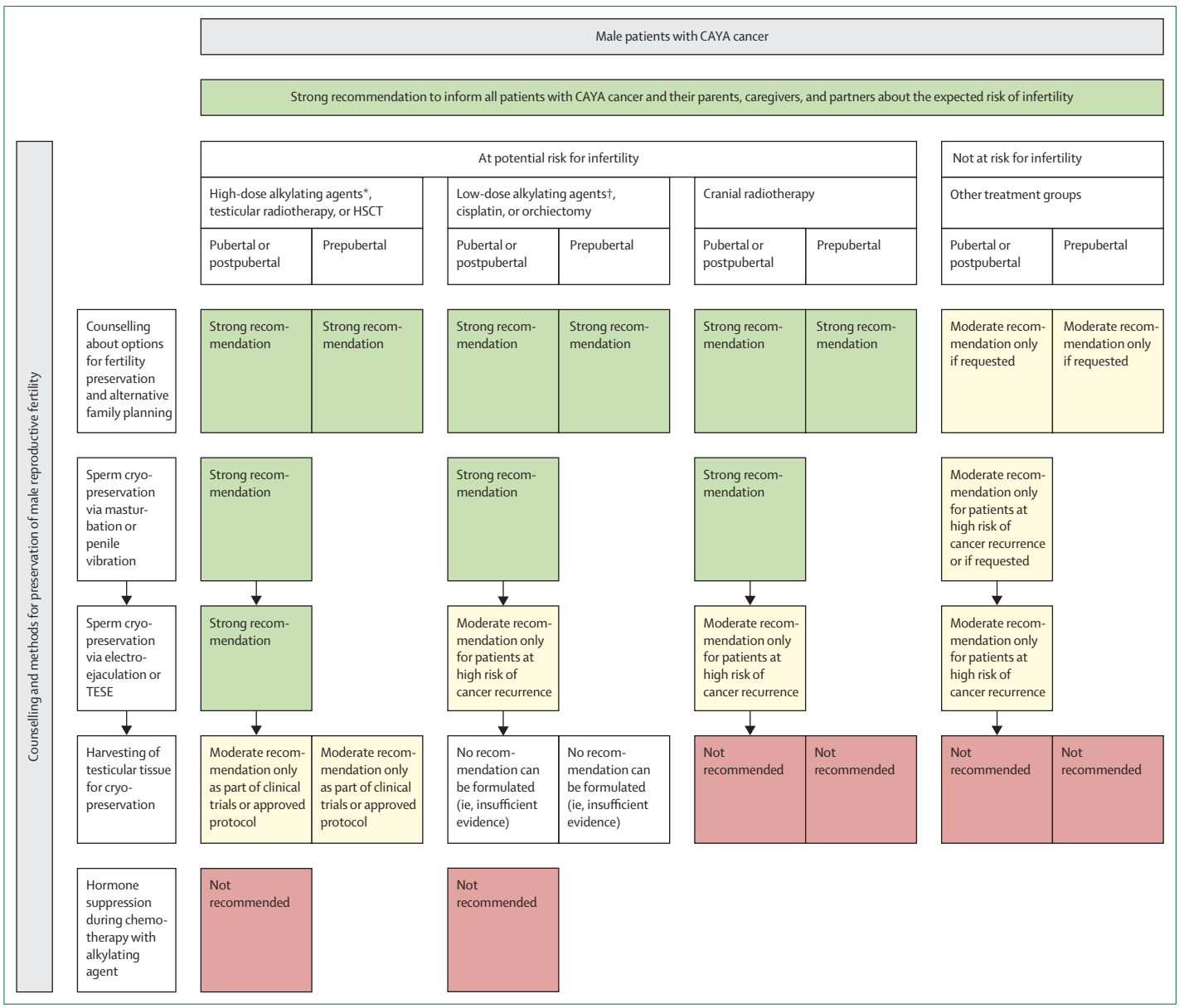

Figure 2: **Recommendations for preservation of reproductive fertility for male patients with CAYA cancer**
Colours represent the strength of recommendation for each method on the basis of the evidence (where green indicates strong recommendation, yellow indicates moderate recommendation, and red indicates that a method is not recommended), corresponding to colours used in previous International Late Effects of Childhood Cancer Guideline Harmonization Group publications Arrows indicate the flow of treatment when methods are not successful or possible. For further details on recommendations see appendix pp 41–42. CAYA=childhood, adolescent, and young adult. HSCT=haematopoietic stem-cell transplantation. TESE=testicular sperm extraction. *Cyclophosphamide-equivalent dose ≥4000 mg/m². †Cyclophosphamide-equivalent dose <4000 mg/m².

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No studies meeting the inclusion criteria were identified that examined the risk of impaired spermatogenesis after platinum compounds. Treatment with platinum compounds showed no significant association with testosterone deficiency (very low-quality evidence).[5] One study showed a reduced likelihood of siring a pregnancy after cisplatin (low-quality evidence).[36]

Treatment with imatinib showed no significant association with low testosterone concentration (low-quality evidence).[37] No reports were identified that investigated the effects of novel agents on the risk of impaired spermatogenesis.

There is very low-quality to high-quality evidence for an increased risk of impaired spermatogenesis and testosterone deficiency in survivors of CAYA cancer after radiotherapy to volumes exposing the testes (hereafter referred to as testicular radiotherapy).[5,33,35,38] One study showed a reduced likelihood of siring a pregnancy after higher than 7·5 Gy radiotherapy to the testes compared with no radiotherapy (low-quality

evidence).[3] The radiation threshold dose for testosterone deficiency is expected to be higher than 7·5 Gy; the risk substantially increased after doses of 12·0 Gy and higher.[5,35]

An association between increasing doses of cranial radiotherapy and the risk of hypogonadotropic hypogonadism was identified (moderate-quality evidence).[39,40] Additionally, there was no significant effect of cranial radiotherapy and dose on the likelihood of siring a pregnancy or livebirth (moderate-quality evidence).[3,41]

No studies were identified evaluating the risk of ejaculation disorders in survivors of CAYA cancer after treatment with orchiectomy, retroperitoneal lymph node dissection, or genitourinary surgery. Similarly, no studies were found that investigated the risk of obstructive azoospermia in survivors of CAYA cancer who were treated with retroperitoneal lymph node dissection or major surgery to the deep pelvis.

An association between older age at cancer treatment and risk for impaired spermatogenesis was identified among CAYA cancer survivors in one study (low-quality evidence),[42] whereas two other studies did not support this association.[34,43] No significant association was found between age at treatment and testosterone deficiency.[35,44,45]

Recommendations

The evidence is scarce regarding a dose threshold for alkylating agents, with the most robust data reporting that azoospermia was unlikely after a cyclophosphamide-equivalent dose less than 4000 mg/m².[43] The panel therefore defined a high alkylating agent dose as a cyclophosphamide-equivalent dose at or above 4000 mg/m² and a low alkylating agent dose as cyclophosphamide-equivalent dose less than 4000 mg/m². Patients who are treated with testicular radiotherapy or haematopoietic stem cell transplantation (HSCT), or both, are at increased risk of infertility as well. Additionally, considering expert opinions and evidence from adult cancer survivors and young adult and adult testicular cancer survivors, the panel recognises that patients who are treated with cisplatin or orchiectomy, or both, are at potential risk of infertility.[46,47] Patients treated with cranial radiotherapy are at risk for infertility as well. Although gonadal function is not affected, spermatogenesis can be impaired by damage to the hypothalamic–pituitary axis. Although sperm production can be stimulated by use of hormonal therapy when paternity is desired, the panel agreed that these patients should be counselled about fertility preservation.

The panel strongly recommends that health-care providers discuss options for fertility preservation and alternative family planning with patients with CAYA cancer and their families if planned treatment will include alkylating agents of any dose (high-quality evidence), testicular radiotherapy (moderate-quality evidence), HSCT (expert opinion), cisplatin (low-quality evidence), orchiectomy (expert opinion), or cranial radiotherapy (very low-quality evidence), or a combination.

The panel also agreed that the choice of who should discuss fertility preservation and options for family planning with the patients with CAYA cancer and their families should depend more on the provider's knowledge, patient's disease state, and local access to fertility specialists, rather than identifying a particular discipline to assume this role. Possibilities include a paediatric oncologist, endocrinologist (including paediatric endocrinologist), andrologist, fertility specialist, specialised nurse, or other relevant health-care provider. Importantly, a system should be in place that specifies the clinician, or clinicians, who are responsible for providing information about infertility risk, options for fertility preservation, and their costs and logistics to patients and their families shortly after diagnosis. Documentation of these discussions is important. A fertility unit in the same hospital of the oncology unit is not mandatory to discuss fertility preservation, but multidisciplinary networks (ie, oncofertility working groups) are essential to optimise timely referral.[48]

The panel concurred that if planned treatment will not include gonadotoxic modalities, patients with CAYA cancer and their families should be advised of the benefits and harms of fertility preservation within the context of their personal low risk of infertility and taking into account the risk of cancer recurrence or disease progression (ie, absence of response to initial therapy) that might lead to a potential future need for gonadotoxic therapy. For patients who are at low risk of infertility, referral to a specialist to discuss options for fertility preservation and family planning could be considered on the request for additional information (we moderately recommend referral, although there were no studies to support this option).

What methods for reproductive preservation are appropriate to offer in counselling?

Evidence concerning methods for fertility preservation

There is moderate-quality evidence that sperm quality and yield are sufficient for cryopreservation in patients with CAYA cancer who can produce semen samples by masturbation before cancer treatment.[49–53] In two of these studies, sperm motility decreased after thawing of cryopreserved sperm (moderate-quality evidence).[50,51] Although sperm cryopreservation is an established method of fertility preservation, data on livebirths are limited to sperm obtained from patients with cancer who are older than 25 years and patients without cancer. Evidence cited in existing guidelines reported pregnancies (success rates ranging from 20% to 72%) and livebirths from cryopreserved sperm,[18] including pregnancies with sperm that was stored for up to 28 years.[19–22] Studies about birth outcomes that are related to cryopreserved sperm, specifically for patients with CAYA cancer, are scarce. We identified reports of two livebirths after 13 inseminations of cryopreserved sperm obtained by masturbation, but it was unclear

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from the study whether the livebirths were from a patient with CAYA cancer or a patient with cancer who was older than 25 years (very low-quality evidence).[51] No studies reported pregnancies or livebirths after sperm cryopreservation via penile vibration in patients with CAYA cancer. Additionally, no studies were found to have evaluated complications after sperm cryopreservation through masturbation or penile vibration.

Patients with CAYA cancer who produced semen samples through electroejaculation were reported to have diminished sperm count and motility for cryopreservation (very low-quality evidence).[49,52,54] No studies were identified describing the quality and yield of sperm after testicular sperm extraction. Evidence cited in existing guidelines identified case reports and small case series noting successful sperm collection after rectal electroejaculation under anaesthesia and testicular sperm extraction.[20,21] Additionally, success rates after rectal electroejaculation were similar to standard sperm banking via masturbation for patients with CAYA cancer.[20,21] Three livebirths were reported after testicular sperm extraction combined with intracytoplasmic sperm injection in two (22%) of nine patients with CAYA cancer (very low-quality evidence).[55] No studies reported pregnancies or livebirths after sperm cryopreservation via electroejaculation in patients with CAYA cancer. Additionally, two studies observed no complications after electroejaculation[54] or testicular sperm extraction[55] (very low-quality evidence).

In four studies in which 68–100% of patients had a malignant diagnosis, mature sperm, spermatogonia, and spermatogonial germ cells were observed in dissection of testicular tissue from prepubertal and pubertal patients (low-quality evidence).[56–59] Additionally, there is low-quality evidence of complications after dissection of testicular tissue, including three male patients with a wound infection, one patient with postoperative bleeding, one patient with ipsilateral epididymo-orchitis, one patient with ipsilateral torsed appendix testis, and one patient with scrotal cellulitis.[56,57,59,60] Evidence cited in existing guidelines also reported no major complications after collection of testicular tissue but mentioned the risk of reseeding malignant cells.[22]

No transplantation of spermatogonial stem cells or testes xenografting have been done for patients with CAYA cancer. There are no studies that describe a human livebirth as a result of using cryopreserved testicular tissue as a source of sperm; therefore, this method is considered to be experimental.[19–21,23,24]

No studies were identified that investigated the effects of hormonal gonadoprotection during chemotherapy among male patients with CAYA cancer. Studies cited in existing guidelines reported no significant effect of hormonal gonadoprotection during chemotherapy in reducing the risk of infertility.[20,21,23]

Recommendations

The recommendations for male patients with CAYA cancer who are at potential risk of infertility due to high-dose alkylating agents (ie, cyclophosphamide-equivalent doses ≥4000 mg/m²), testicular radiotherapy, or HSCT are given here. The panel emphasised that shared decision-making between health-care providers and patients and their families is essential when decisions are made about fertility preservation (for any method) and future family planning. It is important to inform patients and their families about the potential benefits, harms, costs, and logistics that are associated with fertility preservation for them to make a well informed decision.

Regarding sperm cryopreservation following masturbation or penile vibration, the panel considered the effectiveness of collection, cryopreservation, and storage and the non-invasiveness of the collection method. However, the subsequent need for assisted reproductive techniques (ie, in-vitro fertilisation or intracytoplasmic sperm injection) with the associated costs, variable success rates after insemination of thawed cryopreserved sperm, the costs for obtaining and storing specimens, and the logistics regarding the subsequent use or the disposal of specimens was also recognised. The panel acknowledged the possibility of religious, cultural, or psychosocial barriers to masturbation in some patients and families and that facilities (eg, hospitals and private clinics) and access to storage might be limited by spatial or financial restrictions. Overall, the panel's view was that the potential benefits of sperm cryopreservation outweigh the harms. For this reason, we strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and postpubertal patients whose treatment will include high-dose alkylating agents or testicular radiotherapy (very low-quality evidence and evidence cited in existing guidelines).

Despite the moderate invasiveness of sperm collection by electroejaculation or testicular sperm extraction, the associated potential risks of the invasiveness, and the need for local or general anaesthesia, the panel considered that the benefits most likely outweigh the potential harms if having biological offspring is strongly desired. When masturbation or penile vibration is not possible or successful, we strongly recommend offering sperm collection through electroejaculation or testicular sperm extraction to pubertal or postpubertal patients (very low-quality evidence and evidence cited in existing guidelines).

Regarding the experimental technique of cryopreservation of testicular tissue from prepubertal patients, the panel acknowledged that this procedure is invasive, that malignant cells could be reintroduced if testicular tissue is reimplanted, that no cryopreserved testicular tissue has ever been transplanted in patients with CAYA cancer before, and thus no human livebirths have occurred by use of this method. However, the panel agreed

that the benefits of future fertility in the setting of improved technology could be worth the costs involved in fertility preservation (ie, need for anaesthesia, surgical procedure, and tissue storage) in patients who are at high risk of infertility. Additionally, implementation of this procedure in a research setting is feasible depending on the infrastructure of the hospital, clinical storage of cryopreserved tissues, and availability of suitable research facilities. Moreover, it is the only method for fertility preservation that is available for prepubertal boys. Overall, the panel concurred that, in the absence of suitable alternatives for fertility preservation, the potential benefits for tissue collection and cryopreservation probably outweigh the potential harms. We therefore moderately recommend offering cryopreservation of testicular tissue for prepubertal patients who are at the highest risk of infertility (ie, patients who will be treated with high-dose alkylating agents, testicular radiotherapy, or HSCT) only as part of clinical trials or in approved protocols and for pubertal and postpubertal patients who cannot undergo other methods for fertility preservation (very low-quality evidence and evidence cited in existing guidelines). It is important to centralise the procedures for cryopreservation of testicular tissue in centres with adequate expertise. The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of a research protocol, recognising the experimental nature of the procedure in prepubertal patients, the insufficient evidence that is available about its efficacy to restore fertility, and the potential risk of reintroduction of malignant cells during autotransplantation of testicular tissue. In pubertal and postpubertal boys, autotransplantation might not be necessary as mature sperm can be extracted from the testicular tissue at the time of collection.

Despite the small costs, feasibility, and ease of implementation, there is no evidence for the effectiveness of hormone suppression as a suitable method for fertility preservation. Therefore, we do not recommend offering hormone suppression to pubertal and postpubertal patients with CAYA cancer (strong recommendation on the basis of evidence cited in existing guidelines).

The recommendations for male patients with CAYA cancer who are at potential risk of infertility due to low-dose alkylating agents (ie, cyclophosphamide-equivalent doses <4000 mg/m^2), cisplatin, or orchiectomy are given here. Despite the lower infertility risk among patients with CAYA cancer in this group compared with patients receiving high-dose alkylating agents, testicular radiotherapy, or HSCT, the panel agreed that the potential benefits outweigh the harms of sperm cryopreservation via masturbation or penile vibration, taking into account the effectiveness of collection, storage, and insemination of sperm, and the non-invasiveness of the collection method. Therefore, offering sperm cryopreservation via masturbation or penile vibration is strongly recommended for patients whose treatment will include low-dose alkylating agents, cisplatin, or orchiectomy (very low-quality evidence and evidence cited in existing guidelines). It is important that patients and families are counselled about the potential risks, logistics, and costs of the procedure to make a well informed decision.

Considering the invasiveness of sperm cryopreservation via electroejaculation and testicular sperm extraction, the potential associated risks of the method, and the need for anaesthesia, the panel agreed that the harms outweigh the benefits for patients in this treatment group. However, as future therapy for disease progression or relapse might include gonadotoxic treatments, the panel concurred that electroejaculation or testicular sperm extraction can be beneficial before front-line therapy, as sperm collection at a later stage might not be an option for patients who are considered to be at high risk for cancer recurrence and who cannot undergo sperm cryopreservation via masturbation or penile vibration. In this situation, the panel agreed that the potential benefits probably outweigh the harms. We moderately recommend offering sperm collection by electroejaculation or testicular sperm extraction only to patients at high risk of recurrence and only when masturbation or penile vibration is not successful in retrieving ejaculate (very low-quality evidence and evidence cited in existing guidelines).

Regarding cryopreservation of testicular tissue, the panel concluded that, due to the uncertainty of the future benefits and the lower infertility risk in this treatment group compared with patients receiving high-dose alkylating agents, testicular radiotherapy, or HSCT, the overall balance of potential harms and benefits is uncertain. Therefore, no recommendation can be made (insufficient evidence).

The recommendations for male patients with CAYA cancer who are at potential risk of infertility due to cranial radiotherapy are given here. High-dose cranial radiotherapy can impair spermatogenesis by interrupting the hypothalamic–pituitary–testicular hormonal axis (ie, hypogonadotropic or central hypogonadism). In this case, when paternity is desired, sperm production can be stimulated by use of pulsatile gonadotropin-releasing hormone or pituitary hormonal therapy (ie, gonadotropin therapy with follicle stimulating hormone and human chorionic gonadotropin). Considering the non-invasiveness of sperm collection by masturbation or penile vibration, postpubertal patients who are at risk for central hypogonadism might benefit from upfront cryopreservation of semen to avoid the need for exogenous gonadotropin therapy at a later stage. However, cryopreserved sperm can be used only for assisted reproduction, whereas spontaneous pregnancy can be pursued following induction of spermatogenesis with gonadotropins. The panel agreed that the potential benefits outweigh the harms and, therefore, we strongly recommend offering sperm cryopreservation via masturbation or penile vibration to postpubertal patients whose treatment will include high-dose cranial radiotherapy (evidence cited in existing guidelines).

Regarding electroejaculation, testicular sperm extraction and testicular tissue cryopreservation, the panel agreed that the potential harms outweigh the benefits, taking into account that the potential for sperm production is not affected in patients with hypogonadotropic hypogonadism and the invasiveness of the procedures. However, for patients who are at high risk of recurrence and might need gonadotoxic treatment in the future, the panel agreed that electroejaculation or testicular sperm extraction could be beneficial upfront as sperm collection at a later stage might not be an option. In this situation, the potential benefits probably outweigh the harms. Therefore, we moderately recommend offering sperm cryopreservation via electroejaculation or testicular sperm extraction to only patients at high risk of recurrence who cannot undergo sperm cryopreservation via masturbation or penile vibration (very low-quality evidence and evidence cited in existing guidelines).

Because of the uncertainty of the future benefits and the fact that the testes are not directly injured during cranial radiotherapy, we do not recommend offering cryopreservation of testicular tissue to prepubertal, pubertal, or postpubertal patients in this treatment group (very low-quality evidence and evidence cited in existing guidelines).

The recommendations for male patients with CAYA cancer who are not at risk of infertility due to other therapies are given here. Although there is no evidence for adverse effects of treatments other than alkylating agents, testicular radiotherapy, cisplatin, orchiectomy, and cranial radiotherapy, the panel concluded that the benefits of sperm cryopreservation via masturbation or penile vibration probably outweigh potential harms for any patient who wishes to do so. Therefore, we moderately recommend offering sperm cryopreservation via masturbation or penile vibration to any patient on the basis of their wishes and shared decision making with their health-care provider (very low-quality evidence and evidence cited in existing guidelines).

Regarding sperm cryopreservation via electroejaculation or testicular sperm extraction, the panel agreed that the benefits of upfront sperm collection probably outweigh the harms in only patients who are at high risk of recurrence and might need gonadotoxic treatment in the future. We moderately recommend offering sperm cryopreservation via electroejaculation or testicular sperm extraction to only patients who are at high risk of recurrence and who cannot undergo sperm cryopreservation via masturbation or penile vibration (very low-quality evidence and evidence cited in existing guidelines).

Due to their perceived low risk of infertility, the invasiveness of the procedure, and the uncertainty of the future benefits, the panel agreed that the potential harms of cryopreservation of testicular tissue outweigh the benefits. Therefore, we do not recommend offering cryopreservation of testicular tissue to prepubertal, pubertal, and postpubertal patients in this treatment group (very low-quality evidence and evidence cited in existing guidelines).

Discussion

We present a systematic review of the evidence and recommendations for optimising counselling for and use of fertility preservation in male patients who are diagnosed with CAYA cancer. This CPG harmonises efforts across Europe, North America, Australia, and New Zealand. The global dissemination of this guideline aims to assist health-care providers in effectively communicating infertility risk to and facilitating informed decision making regarding options for fertility preservation for male patients with CAYA cancer and their families. Additionally, we identified major gaps in knowledge and future directions for research (panel). This CPG, together with the first paper in this Series,[61] focusing on fertility preservation for female patients with cancer, and the third paper in this Series,[62] focusing on guidance for communicating with patients and their families about fertility preservation and its associated ethical issues, is one of three CPGs that we have developed about fertility preservation for patients with CAYA cancer.

Male patients with CAYA cancer who will be treated with alkylating agents, testicular radiation, HSCT, cisplatin, cranial radiotherapy, or unilateral orchiectomy, or a combination, are at potential risk for infertility and should, therefore, be counselled about options for fertility preservation. Patients who will be treated with bilateral orchiectomy will, by definition, become infertile and are therefore qualified for any of the options for fertility preservation.

For some clinical questions that are related to the risk of infertility, there is an absence of evidence. For example, we identified no evidence that alkylating agents independently increase the risk of permanent gonadotoxicity in patients with CAYA cancer. van Beek and colleagues[42] showed no significant effect of epirubicin, bleomycin, vinblastine, and dacarbazine and doxorubicin, bleomycin, vinblastine, and dacarbazine regimen on sperm concentration and Tromp and colleagues[63] reported no significant association with testosterone concentrations. Additionally, Green and colleagues[3] observed that daunorubicin was not significantly associated with a reduced likelihood of siring a pregnancy. Moreover, members of the guideline panel reported no clinical experience to support the notion that anthracyclines increase the risk of permanent gonadotoxicity in patients with CAYA cancer. Consequently, we based our recommendations on available evidence in the published literature and clinical experience with our target population.

Regarding fertility preservation procedures, this CPG includes offering sperm cryopreservation not only to postpubertal males but also to pubertal males. Even among young pubertal patients and patients with small testicular volumes, collection of a semen specimen that is acceptable for cryopreservation is feasible before

gonadotoxic treatment.[49,64,65] This feasibility is especially important as previous reports have shown that sperm cryopreservation in male adolescents with cancer is underused.[66,67] In line with previous guidelines,[19,21,22,24] we moderately recommend offering harvesting testicular tissue for cryopreservation and storage as a method for fertility preservation within the context of an approved research protocol for patients who are at high risk of infertility. Although this fertility preservation technique is experimental in prepubertal patients, the procedure has the potential to be coupled with other interventions that require general anaesthesia[68] and its future use is promising.[60,69,70] A caveat, however, is the potential risk of reintroduction of malignant cells during autotransplantation of testicular tissue, especially for survivors of leukaemia, non-Hodgkin lymphoma, and metastasised solid tumours.[71]

The strength of the CPG in this paper lies in the wide geographical representation of the working group members, the international collaboration, and the multidisciplinary expertise that is needed to derive consensus and facilitate applicability of the recommendations across diverse institutions providing care for patients with CAYA cancer. Application of rigorous GRADE methodology,[26] in combination with the previously published CPG of the IGHG,[5] facilitated a transparent and systematic approach to guideline development. We also involved two patient representatives to ensure that the patient views were considered in the process of guideline development. As this is a rapidly changing field, both in technologies and in patients' acceptance, comprehensive periodic updates of the CPG are planned by the IGHG. Acknowledging that the recommendations in this CPG will be subjected to specific country legislation, we have carefully formulated recommendations to facilitate implementation in diverse settings. This CPG aims to make fertility preservation accessible to all male patients with CAYA cancer.

The CPG is limited by the scarcity of high-quality research data identified in the review. The panel reviewed additional evidence from high-quality existing CPGs that included study populations who were older than 25 years at diagnosis and patients without cancer and presented this information separately to ensure transparency in the process for guideline development.

Conclusion

As part of the international EU-funded project, PanCareLIFE, and in collaboration with IGHG, we have developed a transparent and rigorous CPG to optimise fertility preservation for male patients with CAYA cancer that carefully balances the harms and benefits of methods for fertility preservation for different treatment risk groups. Because evidence related to reproductive technologies is rapidly evolving, the recommendations reflect the current state of reproductive sciences. Implementation of this CPG aims to support patients' desire for biological offspring. Health-care professionals are encouraged to tailor these recommendations to their patients' needs. With this CPG, we ultimately expect to increase future international collaborative research that addresses knowledge deficits that are relevant to male oncofertility and to enhance patients' and their families' quality of life.

Panel: Gaps in knowledge and directions for future research

Effects of cancer treatments for male patients with childhood, adolescent, and young adult cancer

Risks of, and dose thresholds for, impaired spermatogenesis or testosterone deficiency after:

- Busulfan, chlorambucil, cyclophosphamide, ifosfamide, chlormethine, melphalan, or thiotepa (ie, classical bifunctional alkylating agents)
- Dacarbazine, procarbazine, or temozolomide (ie, triazenes)
- Carboplatin, cisplatin, or oxaliplatin (ie, platinum agents)
- Carmustine or lomustine (ie, nitrosoureas)
- Radiotherapy involving exposure of the testes, including patients who are treated with total body irradiation
- Cranial radiotherapy
- Unilateral orchiectomy
- Tyrosine-kinase inhibitors
- Demethylating agent
- Radioactive iodine (ie, ^{131}I)
- Haematopoietic stem-cell transplantation
- Genetic susceptibility, considering that some male survivors of childhood, adolescent, and young adult cancer are azoospermic even after low-dose exposure and some maintain normal sperm counts (ie, >15 000 000 sperm per mL) after high-dose exposures

Risks of ejaculation disorders and obstructive azoospermia after:

- Orchiectomy, retroperitoneal lymph node dissection, or genitourinary surgery

Methods for fertility preservation in male patients with childhood, adolescent, and young adult cancer who are at risk of infertility

Pregnancy outcomes and livebirths after:

- Sperm cryopreservation via masturbation, penile vibration, electroejaculation, or testicular sperm extraction
- Cryopreservation and transplantation of testicular tissue
- Hormonal gonadoprotection

Quality and yield of sperm after:

- Sperm cryopreservation via masturbation, penile vibration, electroejaculation, or testicular sperm extraction
- Cryopreservation and transplantation of testicular tissue
- Hormonal gonadoprotection

Complications after:

- Sperm cryopreservation via masturbation, electroejaculation, or testicular sperm extraction
- Cryopreservation of testicular tissue
- Hormonal gonadoprotection

Quality of sperm and length of storage:

- Association between length of sperm storage and quality of cryopreserved sperm or testicular tissue

Contributors

AF-G, RLM, EAHL, MMH, JLe, WJET, LCMK, LBK, and MDvdW contributed to the conception and design of the study. All authors

contributed to the search strategy, data extractions, and interpretation of the data. All authors and collaborators contributed to the formulation of the recommendations. AF-G, RLM, MMH, JLe, WJET, LCMK, LBK, and MDvdW drafted the manuscript; and DMG, EAHL, JLo, RY, JPG, RTM, JB, RS, AA, LSC, AdV, KJ, AL, AM, LN, MD-S, HT, RH, MMvdH-E, HMvS, AMMvP, UD, JdH, EvD-dB, WHW, and collaborators (for full details of the collaborators see the appendix, pp 1–2) critically revised the manuscript. All authors and collaborators approved the final version of this Series paper.

Declaration of interests

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