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Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer 1

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

Renée L Mulder, Anna Font-Gonzalez*, Melissa M Hudson, Hanneke M van Santen, Erik A H Loeffen, Karen C Burns, Gwendolyn P Quinn, Eline van Dulmen-den Broeder, Julianne Byrne, Riccardo Haupt, W Hamish Wallace, Marry M van den Heuvel-Eibrink, Antoinette Anazodo, Richard A Anderson, Anke Barnbrock, Joern D Beck, Annelies M E Bos, Isabelle Demeestere, Christian Denzer, Natascia Di Iorgi, Holly R Hoefgen, Rejin Kebudi, Cornelis Lambalk, Thorsten Langer, Lillian R Meacham, Kenny Rodriguez-Wallberg, Catharyn Stern, Eveline Stutz-Grunder, Wendy van Dorp, Margreet Veening, Saskia Veldkamp, Eline van der Meulen, Louis S Constine, Lisa B Kenney, Marianne D van de Wetering, Leontien C M Kremer†, Jennifer Levine†, Wim J E Tissing†, on behalf of the PanCareLIFE Consortium‡*

Female patients with childhood, adolescent, and young adult cancer are at increased risk for fertility impairment when treatment adversely affects the function of reproductive organs. Patients and their families desire biological children but substantial variations in clinical practice guidelines reduce consistent and timely implementation of effective interventions for fertility preservation across institutions. As part of the PanCareLIFE Consortium, and 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 female patients who were 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. This clinical practice guideline leverages existing evidence and international expertise to develop transparent recommendations that are easy to use to facilitate the care of female patients with childhood, adolescent, and young adult cancer who are at high risk for fertility impairment. A complete review of the existing evidence, including a quality assessment, transparent reporting of the guideline panel's decisions, and achievement of global interdisciplinary consensus, is an important result of this intensive collaboration.

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

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Introduction

5-year survival rates now exceed 80% among patients with childhood, adolescent, and young adult (CAYA) cancer (ie, diagnosed aged ≤25 years), leading to an increasing number of survivors who reach adulthood. Survivors of CAYA cancer value the ability to lead a full reproductive life.[1] However, a substantial proportion of female survivors of CAYA cancer will have compromised reproductive function following cancer treatment, which has been shown to generate high levels of distress among patients and their families.[2–5]

Injury to the reproductive system in female survivors of CAYA cancer can manifest as premature ovarian insufficiency and infertility.[6] Premature ovarian insufficiency leads to infertility, but the oestrogen deficiency that is associated with premature ovarian insufficiency can also affect the uterus growth; the risk of osteoporosis, cardiovascular disease, and impaired cognitive function; wellbeing; and sexual health. For prepubertal and peripubertal girls, ovarian insufficiency can also lead to growth impairment, delay in pubertal progression, and loss of self-esteem.[7] Although fertility management for cancer has emerged as an important issue in the clinical setting, previous research indicates that patients with CAYA cancer, especially females, are not always adequately counselled about the potential adverse effects of cancer treatment on reproductive function and options for fertility preservation, nor are they referred to specialists for fertility preservation.[8,9]

A previous report showed that existing clinical practice guidelines (CPGs) for fertility preservation that were developed by different groups and institutions vary substantially and only about one-third of guidelines are derived by use of rigorous methods.[10] To facilitate global consensus regarding this topic, the EU-funded project, PanCareLIFE, in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), organised a multidisciplinary group of international experts to develop a transparent evidence-based CPG for fertility preservation in female patients with CAYA cancer.[11,12] We provide a systematic review and recommendations for fertility preservation in female patients who are diagnosed with CAYA cancer.

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Data collection

Guideline panel formation

A multidisciplinary panel of 36 international specialists in paediatric oncology and haematology, radiation oncology, endocrinology (including paediatric endocrinology), reproductive medicine, gynaecology, psychology, epidemiology, and guideline methodology was convened (appendix pp 1–2). Members were selected (by MMH, LBK, MDvdW, LCMK, JL, and WJET) because of their experience, publications, 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 infertility and options for fertility preservation to both female 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) and to provide guidance about how and when to offer fertility preservation treatment. Females who had reached menarche were considered to be postpubertal. The guideline panel defined premature ovarian insufficiency as an outcome that could lead to impaired fertility. The standard definitions of gonadotoxic treatment modalities and outcomes are reported 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 methods for reproductive preservation are appropriate to offer in counselling of prepubertal, peripubertal, and postpubertal female patients with CAYA cancer (appendix pp 6–8). Formulation of the clinical questions was based on discordant areas in recommendations that were identified in existing CPGs for fertility preservation in patients with CAYA cancer, as described by Font-Gonzalez and colleagues,[10] and from 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 9–15).

Search strategy and selection criteria

We updated previous IGHG recommendations regarding who should be informed about potential infertility risk.[13] 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", "female", "chemotherapy", "radiotherapy", "stem cell transplant", "POI", "live births", "fertility preservation". We reviewed only reports that were published in English. Eligible study populations for the working group on risk assessment were female patients with cancer, in which 75% or more of patients had been diagnosed with cancer aged 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. Sample size restrictions were not applied when assessing novel agents (eg, monoclonal antibodies and tyrosine-kinase inhibitors). Eligible study outcomes were premature ovarian insufficiency, central hypogonadism, livebirths, and pregnancy. For the working group on methods for fertility preservation, eligible study populations included 75% or more female patients diagnosed with CAYA cancer. Eligible outcomes included livebirths, pregnancy complications (eg, stillbirth, premature birth, and low gestational age), premature ovarian insufficiency, and complications of methods for fertility preservation that were related to the patients and their offspring.

Due to few data that were available on methods for fertility preservation, additional evidence cited in existing high-quality evidence-based guidelines for fertility preservation, identified by Font-Gonzalez and colleagues,[10] was included without restriction to cancer diagnoses at age 25 years or younger (hereafter referred to as existing guidelines).[14–20] Experts were consulted to establish whether additional evidence was missing, and references of relevant literature reviews and reports were crosschecked.

Studies were independently selected by the primary reviewers (AF-G, RLM, and EAHL) and crosschecked by the 23 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 assessed by use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[21]

Recommendations

GRADE Evidence to Decision frameworks were used to formulate recommendations in a systematic and transparent manner.[22] 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 16).[23,24] When we identified low-quality evidence or no evidence, the recommendation was based on existing guidelines[14–20] and expert opinions from the guideline panel. 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 then critically appraised by three independent external experts (Anja Borgmann-Staudt, Teresa Woodruff, and Yasmin Jayasinghe; appendix p 2)

and three patient or survivor representatives (EvdM, Alexandra Brownsdon, and Joyce Reinecke; appendix p 2). All experts and survivors agreed with the formulated recommendations. Wording of some 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 6383 articles identified, 526 underwent full-text review and 45 articles were eligible for inclusion, including evidence described in the previous IGHG publication[13] (figure 1). The tables containing conclusions of evidence and the Evidence to Decision frameworks are presented in the appendix (pp 20–37). The recommendations are presented in figure 2 and the appendix (pp 38–41). We present the evidence and recommendations for the three key clinical questions that were described.

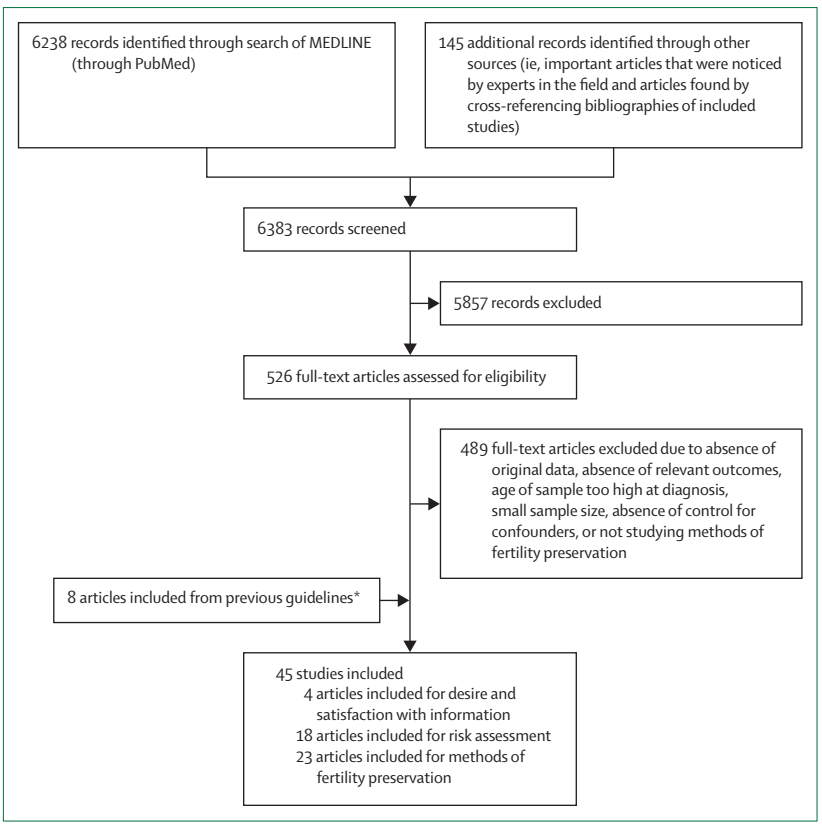

Figure 1: **Flow diagram for selection of studies**
*International Late Effects of Childhood Cancer Guideline Harmonization Group clinical practice guideline for surveillance of premature ovarian insufficiency.[13]

Who should be informed about potential infertility risk?

Evidence concerning desire for and satisfaction with information

Moderate-quality evidence showed that most patients with cancer and their families were not satisfied with the content of fertility-related discussions provided by oncology health-care professionals. In particular, there was dissatisfaction with the information provided about fertility risks, options to preserve fertility, and alternative family planning.[25,26]

Low-quality evidence showed that postpubertal patients with cancer strongly desire information about the effects of cancer treatment on fertility and options for fertility preservation.[27] 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).[28]

Recommendations

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

Who should be counselled about fertility preservation?

Evidence concerning risk groups

Based on previously published IGHG and newly published data, there is high-quality evidence that alkylating agents are associated with premature ovarian insufficiency in a dose-dependent manner in survivors of CAYA cancer.[13,29–37] When assessing individual alkylating agents, we noted an increased risk of premature ovarian insufficiency with increasing doses of procarbazine[13,32,34,36] (high-quality evidence) and cyclophosphamide[13,29–32,36] (moderate-quality evidence). Additionally, we identified an increased risk of premature ovarian insufficiency after treatment with busulfan, but the dose–response relationship was unclear (low-quality evidence).[31,33]

There is low-quality evidence for a decreasing likelihood of pregnancy or live birth after increasing doses of cyclophosphamide,[38–40] busulfan,[38] and lomustine.[38,39] No significant effect was identified for the association of ifosfamide (low-quality evidence),[38] procarbazine (moderate-quality evidence),[38–40] or chlormethine (low-quality evidence)[39] with the likelihood of pregnancy and live birth. No studies were identified that evaluated the risk of premature ovarian insufficiency after antimetabolites, platinum compounds, anthracyclines, bevacizumab, high-dose etoposide, and novel agents (ie, monoclonal antibodies or tyrosine-kinase inhibitors).

There is high-quality evidence that increasing doses of radiotherapy to volumes exposing the ovaries (hereafter referred to as ovarian radiotherapy) increases the risk of premature ovarian insufficiency in survivors of CAYA cancer.[13,30–37,41,42] Treatment with a combination of alkylating agents and ovarian radiotherapy increases the risk of premature ovarian insufficiency compared with that associated with each method alone (moderate-quality evidence).[13,34,35] There is moderate-quality evidence that

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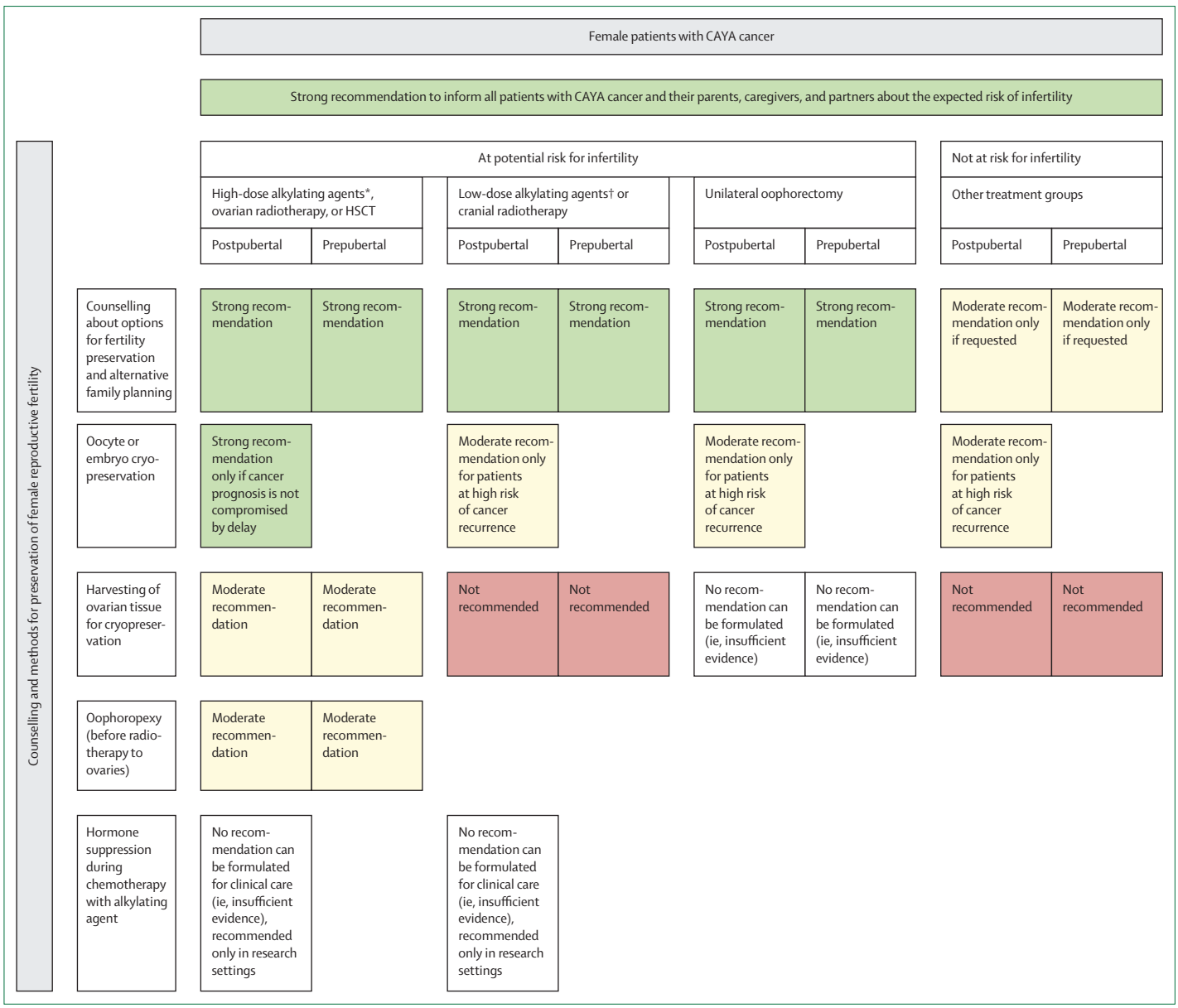

***Figure 2*: Recommendations for preservation of reproductive fertility for female patients with CAYA cancer**
Colours represent the strength of recommendation for each method on the basis of the evidence (where green indicates strong recommendation, yellow indicates moderate recommendation, and red indicates that a method is not recommended), corresponding to colours used in previous International Late Effects of Childhood Cancer Guideline Harmonization Group publications. For further details on recommendations see appendix pp 40–41. CAYA=childhood, adolescent, and young adult. HSCT=haematopoietic stem-cell transplantation. *Cyclophosphamide-equivalent dose ≥6000–8000 mg/m². †Cyclophosphamide-equivalent dose <6000–8000 mg/m².

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increasing doses of ovarian radiotherapy reduce the likelihood of pregnancy and livebirths.[39,40,43]

We identified very low-quality evidence that there is an increased risk of premature ovarian insufficiency after haematopoietic stem-cell transplantation (HSCT). This increased risk is independent of the risk that is conferred by alkylating agents or ovarian radiotherapy, or both, in survivors of CAYA cancer.[36]

There is low-quality evidence that unilateral oophorectomy increases the risk of premature ovarian insufficiency in survivors of CAYA cancer.[32,36] Additionally, we identified very low-quality evidence to suggest no significant effect of oophoropexy in relation to premature ovarian insufficiency risk[35] or likelihood of pregnancy.[39]

We identified an association between increasing doses of cranial radiotherapy[44] and the risk of hypogonadotropic hypogonadism (moderate-quality evidence) and reduced likelihood of pregnancy in survivors of CAYA cancer (low-quality of evidence).[39,43] There is low-quality evidence that, among CAYA cancer survivors, patients who are

older at cancer treatment have a higher risk for premature ovarian insufficiency compared with patients who are younger.[13,30–33,35,36,41,42]

Recommendations

Evidence was scarce regarding a dose threshold for the effect of alkylating agents on fertility. Studies reported no significantly increased risk of premature ovarian insufficiency after cyclophosphamide-equivalent doses at or lower than 6000 mg/m²,[36] 8000 mg/m²,[35] and 12 000 mg/m².[37] Considering these data, the panel concluded that there is a high risk of premature ovarian insufficiency after cumulative doses of alkylating agent at or above the range of 6000–8000 mg/m² and a low risk of premature ovarian insufficiency for less than this range. Patients who are treated with ovarian radiotherapy are also at increased risk of premature ovarian insufficiency (high-quality evidence). Additionally, the panel recognises that patients who are treated with HSCT and unilateral oophorectomy are at potential risk of impaired fertility. Patients who are treated with cranial radiotherapy are at risk for infertility as well. Although gonadal function is not affected, ovarian function can be impaired by damage to the hypothalamic–pituitary axis. Although the ovaries can be stimulated by use of hormonal therapy when pregnancy is desired, the panel agreed that patients who will be treated with cranial radiotherapy should be counselled on 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), ovarian radiotherapy (high-quality evidence), HSCT (very low-quality evidence), unilateral oophorectomy (very low-quality evidence), cranial radiotherapy (very low-quality evidence), or a combination. The panel also agreed that the choice of who should discuss options for fertility preservation and family planning with 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), fertility specialist, specialised nurse, or another relevant health-care provider. Importantly, at each individual institution, a system should be in place that clearly specifies the clinician, or clinicians, who are responsible for providing information about infertility risk and options for fertility preservation to patients and their families shortly after diagnosis, which includes information on costs and logistics. 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.[45]

The panel concurred that if planned treatment will not include gonadotoxic modalities, then patients with CAYA cancer and their families should be advised of the benefits and harms of fertility preservation within the context of their personal risk. They should also consider 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

We identified no studies of livebirths in postmenarcheal female survivors of CAYA cancer who were aged 25 years or younger tat the time of oocyte or embryo cryopreservation. Evidence cited in existing guidelines did report livebirths in survivors of CAYA cancer older than 25 years at the time of cryopreservation.[20] Although the success rates for pregnancy and livebirths are generally better with fresh oocytes compared with cryopreserved oocytes,[46] some reproductive specialty centres have reported similar success rates, especially in women who became pregnant when they were young.[14–16,20] 20 cases of oocyte harvesting at ages 13–20 years before gonadotoxic treatment have been described.[47]

The most relevant potential harm that is related to oocyte or embryo cryopreservation for patients with CAYA cancer is the delay in initiating treatment and concern for the subsequent effect of the delay on disease-free survival. Additionally, studies cited in existing guidelines noted increased risks for patients who were medically unstable (eg, unable to tolerate an anaesthetic and collection of oocytes) and undergoing in-vitro fertilisation, which were related to anaesthesia and oocyte collection procedure, including haemorrhage, thrombosis, and infection.[17] However, other literature supports the safety of the procedure on the basis of shortening the delay in initiation of cancer treatment with new techniques and reducing the development of complications of the procedure.[48]

We identified seven studies that reported ovarian tissue cryopreservation in patients who were diagnosed with a malignant cancer at age 25 years or younger.[49–55] Although livebirths have been reported after ovarian tissue cryopreservation (with an approximate success rate of 45%), it is unclear whether these successes were all from patients who were diagnosed with cancer at age 25 years or younger because age of patients who had livebirths was not reported. At least nine women who were diagnosed with cancer at a young age (ie, ≤25 years) successfully gave birth to 14 healthy babies after

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See **Online** for appendix

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transplantation of cryopreserved tissue.[51,52,54,55] Systematic reviews, including patients with CAYA and adult cancer and patients without cancer, reported 86 livebirths after ovarian tissue cryopreservation, with a corresponding pregnancy rate of 23–37%.[56,57] As of 2017, an estimated 130 livebirths have been achieved.[58] We identified no cohort studies reporting livebirths after prepuberty ovarian tissue cryopreservation and reimplantation. There are four published case reports showing successful grafting of ovarian tissue that was harvested before menarche resulting in two livebirths[59,60] and puberty induction in patients without cancer.[61,62] Evidence cited in existing guidelines reported that endocrine function could be temporally restored after reimplantation of ovarian tissue.[18]

There is very low-quality evidence of complications after ovarian tissue cryopreservation, with three studies reporting intraoperative bleeding in a total of three patients.[49,50,52,53,63–67] We identified 12 patients with contamination in cryopreserved tissue (detected by histological examination and PCR; very low-quality evidence);[50,54,55,68] patients with leukaemia are at especially high risk.[50] No evidence of contamination by malignant cells was observed in cryopreserved tissue from patients with non-metastatic solid tumours and in patients with Hodgkin lymphoma (very low-quality evidence).[49–51,55,63,64,69,70] Evidence cited in existing guidelines did not indicate cancer recurrence from the engrafted tissue in humans,[18] nor pregnancy-related complications in women or congenital abnormalities among offspring of women who underwent transplantation of cryopreserved tissue.[20]

We identified reports of at least 42 livebirths after oophoropexy before radiotherapy exposure (very low-quality evidence).[37,71] However, very low-quality evidence indicates that there is no significant difference in the probability of a live birth before age 40 years among women who did versus women who did not have oophoropexy.[37] We identified one study reporting no significant effect of oophoropexy on the risk of premature ovarian insufficiency in female survivors of CAYA cancer (low-quality evidence).[35]

We identified no studies examining complications of oophoropexy in female patients with CAYA cancer. Evidence cited in existing guidelines supports that oophoropexy does not increase the risk of congenital abnormalities among offspring.[20]

There is very low-quality evidence from a single study that the prevalence of premature ovarian insufficiency is lower among patients with CAYA cancer after receiving analogues of gonadotropin-releasing hormone (GnRH) during cancer treatment as compared with patients who did not.[72] Among female adolescents with cancer who received GnRH analogues, most young women had regular menstrual cycles 1–17 years after the end of treatment (very low-quality evidence).[72,73] From studies cited in several existing guidelines, we identified conflicting evidence about the efficacy of hormone suppression.[14–20] A meta-analysis of individual patient-level data of patients with premenopausal early-stage breast cancer from five major trials showed that concurrent administration of GnRH analogues and chemotherapy significantly reduced the risk of developing chemotherapy-induced premature ovarian insufficiency and was associated with a higher number of pregnancies after treatment.[74]

However, large and well designed randomised controlled trials with a long follow-up (ie, at least until reproductive age) should be done to further investigate the effects of GnRH analogues in preventing chemotherapy-induced premature ovarian insufficiency in young patients (ie, ≤25 years) with CAYA cancer who are treated with paediatric-focused chemotherapy regimens. We identified very low-quality evidence that there are no late complications from hormone suppression in female patients with CAYA cancer.[73] Evidence cited in existing guidelines reported reversible and few adverse events associated with GnRH, such as hot flashes, headaches, sweating, vaginal dryness, and risk of bone-mineral depletion when used for extended periods without oestrogen treatment.[15–17,20]

Recommendations

The recommendations for female patients with CAYA cancer who are at potential risk of infertility due to high-dose alkylating agents (ie, cyclophosphamide-equivalent doses ≥6000–8000 mg/m²), ovarian 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 for future family planning. It is important to inform patients and their families about the potential benefits, harms, costs, and logistics associated with fertility preservation for decisions to be well informed.

The panel identified oocyte and embryo cryopreservation as established methods for fertility preservation in postpubertal women. Pragmatically, most adolescents and young adults (ie, ≤25 years) will opt for oocyte cryopreservation as they are much less likely to be partnered or interested in donor sperm than are older women. The panel noted that the hormone stimulation that is needed for oocyte retrieval can delay initiation of cancer treatment, potentially raising concerns about cancer outcomes if there are any delays. However, the panel also noted that advances in ovarian stimulation allow for oocyte retrieval within approximately 2 weeks from stimulation. Therefore, if the infrastructure for referral to reproductive endocrinology is in place, then delays should be minimal.[75] The panel also recognised the moderately invasive nature of both procedures, the associated psychological harms (eg, distress and anxiety) as described in older populations (ie, aged 25–40 years), and the potential for hormonal side-effects.[76,77] Although an age cutoff for oocyte cryopreservation is difficult to

define, the panel acknowledged the ethical complexities and requirements of physical and emotional maturity of postmenarcheal girls. Additionally, the panel considered the possibility of religious, cultural, or psychosocial barriers to fertility preservation in some patients or families, or both. In some countries, the procedures to harvest oocytes, store oocytes, and implement assisted-reproductive techniques incur substantial costs. Taken together, the optimal method for oocyte preservation can vary according to an individual patient's diagnosis and maturity, clinical status, safety in delaying treatment initiation, and geographical and financial access to reproductive endocrinology services and storage facilities. Overall, the panel's view was that the potential benefits of oocyte or embryo cryopreservation outweigh the potential harms for this group who are at high risk of infertility when delay of therapy is not a concern. An acceptable delay of therapy depends on the disease status of the patient and should, therefore, be determined on an individual basis. We strongly recommend offering oocyte or embryo cryopreservation to postmenarcheal patients with CAYA cancer if prognosis would not be compromised by a delay in treatment initiation (evidence cited in existing guidelines). Due to the immaturity of the oocytes, this method of fertility preservation is not an option for prepubertal and peripubertal girls.

Because the research surrounding the use of ovarian tissue cryopreservation is evolving and the lag time between collection of ovarian tissue and its use for fertility is so long, particularly in prepubertal patients, the panel made a clear distinction between collection and transplantation of ovarian tissue. The panel agreed that the technical risks for the resection of ovarian tissue are small and are risks that are associated with any laparoscopic technique (ie, infection, bleeding, perforation of bowel, bladder, or blood vessel) and undergoing anaesthesia. However, these risks were balanced against the fact that the procedure can be done concurrently with other surgical procedures and that ovarian tissue cryopreservation is the only method for fertility preservation that is available for prepubertal and peripubertal girls and postpubertal women who are unable to undergo oocyte cryopreservation. Fertility preservation for prepubertal girls is ethically complex because there is a scarcity of evidence about the efficacy of ovarian tissue cryopreservation for this age group.[78] The panel agreed that collection of ovarian tissue is ethically justifiable in most circumstances and does not require additional governance. The panel concurred that the benefits of harvesting ovarian tissue probably outweigh the potential harms in this population, who are at high risk of infertility, due to the possible future desire of the patient to have biological offspring. Therefore, we moderately recommend offering ovarian-tissue harvesting for cryopreservation and storage to prepubertal and postpubertal patients as standard care (very low-quality evidence and evidence cited in existing guidelines). Depending on the age of the patient and their disease, ensuring that patients and their families understand the limitations that are associated with future use of the tissue that is preserved is important. To assist clinicians in addressing the ethical complexities in prepubertal girls, support processes for clinical ethics, as described by McDougall and colleagues,[78] can be helpful.

The panel considered autotransplantation as the only mechanism by which cryopreserved ovarian tissue can be used for fertility. The panel agreed that transplantation of postpubertal cryopreserved ovarian tissue can be offered as clinical care but advised careful evaluation of outcomes of the procedure as clinical research. Transplantation of prepubertal cryopreserved ovarian tissue should be offered only in the context of a research protocol due to the experimental nature of this procedure. The panel recognised the potential risk of reintroduction of malignant cells during autotransplantation of ovarian tissue, especially for survivors of leukaemia, non-Hodgkin lymphoma, and metastasised solid tumours, and the scarcity of data concerning transplantation of prepubertal cryopreserved ovarian tissue.

The panel considered oophoropexy as an established procedure that is generally feasible before administration of pelvic radiotherapy. However, the panel also considered that oophoropexy involves an operative procedure under general anaesthesia that has its own associated risks, and there is little evidence of benefit in preserving ovarian function. Therefore, consultation with a radiation oncologist is essential to establish whether oophoropexy will facilitate ovarian shielding during radiotherapy in the context of the patient's pelvic tumours. Despite the anticipated undesirable effects and costs, the panel considered that the potential benefits of oophoropexy probably outweigh the potential harms. We moderately recommend offering oophoropexy before ovarian radiotherapy (very low-quality evidence).

Although hormone suppression for fertility preservation appears to require few resources and is feasible to implement, the panel considered the magnitude of the benefits to be uncertain and concluded that the balance between the potential benefits and harms is uncertain (inconclusive evidence). Therefore, no recommendation for clinical care was formulated, but the panel agreed that hormone suppression could be offered in a research setting. If offered, it should be an adjunct to other procedures for fertility preservation and not a replacement.

The recommendations for female patients with CAYA cancer who are at potential risk of infertility due to low-dose alkylating agents (ie, cyclophosphamide-equivalent doses <6000–8000 mg/m^2), cranial radiotherapy, or unilateral oophorectomy are given here. The panel concluded that, due to the low risk of infertility after cumulative doses of alkylating agent that are less than the range of 6000–8000 mg/m^2, the potential harms of oocyte or embryo cryopreservation probably outweigh the benefits. The panel concluded that the same balance of consequences exists for patients whose treatment will include

cranial radiotherapy. Patients who are exposed to low cumulative doses of alkylating agents should have intact ovarian function following the completion of therapy. Patients facing high-dose cranial radiotherapy require different considerations as their ovaries are intact but do not have pituitary hormonal stimulation. Ovarian function can be supported at the time of family planning by use of pituitary hormonal therapy (ie, follicle stimulating hormone and human chorionic gonadotropin). Oestrogen replacement therapy will be necessary to reach optimal height potential, peak bone mass, and uterine maturation sufficient to support pregnancy. Additionally, although patients whose treatment includes unilateral oophorectomy can be at increased risk for impaired fertility, the benefits of oocyte or embryo cryopreservation do not outweigh potential harms, as these patients will have a healthy remaining ovary. However, as future therapy for disease progression or relapse might include gonadotoxic treatments, the panel concurred that oocyte or embryo cryopreservation could be beneficial before front-line therapy for patients who are considered to be at high risk for cancer recurrence. This benefit could also be relevant for patients with gynaecological germ-cell tumours who underwent adnex extirpation. In this situation, the panel agreed that the potential benefits probably outweigh the harms. Therefore, we moderately recommend offering oocyte or embryo cryopreservation to postmenarcheal patients who are at high risk of recurrence and might need gonadotoxic treatment in the future (evidence cited in existing guidelines).

Because there is a potential risk of premature ovarian insufficiency when removing ovarian tissue, the panel agreed that the potential harms outweigh the benefits for patients who will be treated with low-dose alkylating agents or cranial radiotherapy. Therefore, we do not recommend offering ovarian tissue cryopreservation to these patients (very low-quality evidence and evidence cited in existing guidelines). Regarding unilateral oophorectomy, the panel concluded that the balance between the potential benefits and harms is uncertain due to the absence of data about the risk of premature ovarian insufficiency in the remaining ovary after harvesting ovarian tissue. Therefore, no recommendation can be made.

The recommendations for female patients with CAYA cancer who are not at risk of infertility due to other treatments are given here. As there is no evidence for gonadotoxic effects of treatments other than alkylating agents, ovarian radiotherapy, HSCT, unilateral oophorectomy, or cranial radiotherapy, we only moderately recommend offering oocyte or embryo cryopreservation to postmenarcheal patients who are at high risk of recurrence and might need gonadotoxic treatment in the future (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, female patients who are diagnosed with CAYA cancer. This CPG harmonises efforts across Europe, North America, Australia, and New Zealand. A complete review of the existing evidence, including a quality assessment, transparent reporting of the guideline panels' decisions by use of the GRADE framework, and achievement of global interdisciplinary consensus, is an important result of this intensive collaboration. The global dissemination of this guideline aims to assist health-care providers to effectively care for female patients with CAYA cancer who are at risk for fertility impairment and to facilitate informed decision making by patients and families regarding options for fertility preservation. Additionally, the guideline panel identified major gaps in knowledge and future directions for research (panel). This CPG is one of the three CPGs that we have developed, together with the second paper in this Series,[79] which focuses on fertility preservation for male patients with CAYA cancer, and the third paper in this Series,[80] which focuses on guidance for communicating with patients and families about fertility preservation and its associated ethical issues.

Female patients with CAYA cancer who will be treated with alkylating agents, ovarian radiotherapy, HSCT, cranial radiotherapy, unilateral oophorectomy, or a combination of these treatments, are at potential risk for infertility and should be counselled about options for fertility preservation. Recommendations for specific methods for fertility preservation vary by treatment exposure. Patients who will be treated with bilateral oophorectomy 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 and premature ovarian insufficiency, there is an absense of evidence. Within the CAYA cancer population, we identified no studies meeting our inclusion criteria that investigated anthracyclines as being potentially gonadotoxic. Several reports from the Childhood Cancer Survivor Study evaluated multiple chemotherapeutic agents, including anthracycline agents by univariate analysis, none of which identified anthracyclines as a significant determinant for gonadotoxicity.[36,38] Moreover, van den Berg and colleagues evaluated hormonal and ultrasound markers of ovarian reserve and showed no significant effect of doxorubicin on low antral follicle count.[81] Additionally, members of the panel reported no clinical experience to support the notion that anthracyclines increased the risk of permanent gonadotoxicity in young patients with CAYA cancer. Because data from the adult cancer population cannot be extrapolated to young patients due to differences in pharmacodynamics and physiological ovarian reserve, the recommendations provided in this review are limited to patients with CAYA cancer and based on strong, direct evidence or a strong clinical experience in this population, or both.

This CPG differentiates between the first step of harvesting ovarian tissue for cryopreservation and the

subsequent step of transplantation of cryopreserved ovarian tissue. The panel recognised the potential risk of reintroduction of malignant cells during transplantation of ovarian tissue in survivors of leukaemia, non-Hodgkin lymphoma, and metastatic solid tumours and the scarcity of data on transplantation of prepubertal cryopreserved ovarian tissue. Although promising data have emerged from a case report,[82] tissue contamination is a concern.[83] The literature reflects a debate around ovarian tissue cryopreservation, with some clinicians and researchers arguing that increasing data showing efficacy and safety of the procedure supports its use as a standard-care approach in adult women.[84] A systematic review reported 1019 patients who had ovarian tissue cryopreservation, with ages ranging from 0·4 years to 20·4 years, with 298 patients under the age of 13 years.[47] However, for prepubertal girls, autotransplantation is still investigational while awaiting additional evidence concerning the complex medical and ethical issues in this patient group.[83] A literature review that focused on ovarian tissue cryopreservation among female patients who were younger than 20 years with any diagnosis emphasised the absence of standardisation for removal of ovarian cortical tissue in children. 11 (69%) of 16 patients who underwent transplantation of ovarian tissue had pregnancies, with 56% (nine of 16) of patients having a live birth.[47] Clearly, further refinement of clinical standards for ovarian tissue cryopreservation for patients with CAYA cancer is needed. The rapidly evolving experience with ovarian tissue cryopreservation and subsequent autotransplantation can be expected to address knowledge gaps in this area.

The strength of the present CPG lies in the wide geographical representation and multidisciplinary expertise of the guideline panel and the established international collaboration. In combination with a previously published IGHG CPG,[13] we applied rigorous methods[21] that facilitated a transparent and systematic approach of the processes for guideline development. We also involved patient representatives from different countries to ensure that patient values were considered in the developmental process. An external review of the draft recommendations by international experts in fertility preservation facilitated refinement of the recommendations. Because reproductive technologies are evolving rapidly, the recommendations reflect the current state of reproductive science. Therefore, comprehensive periodic updates of the recommendations are planned by the IGHG. Acknowledging that the recommendations will be subjected to national and institutional legislation and policies, we have carefully formulated recommendations to facilitate implementation in different health-care settings.

Conclusion

As part of the international EU-funded project, PanCareLIFE, and in collaboration with the IGHG, we have developed a transparent and rigorous CPG to optimise fertility preservation for female patients with CAYA cancer that carefully balances the harms and benefits of methods for fertility preservation for different risk groups. In accordance with patients' and their families' strong desire for genetically related children, this CPG aims to make fertility preservation accessible to female patients with CAYA cancer. 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, addressing knowledge deficits that are relevant

Panel: Gaps in knowledge and directions for future research

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

Risks of, and dose thresholds for, premature ovarian insufficiency after:

- Busulfan, chlorambucil, cyclophosphamide, ifosfamide, chlormethine, melphalan, or thiotepa (ie, classical bifunctional alkylating agents)
- Dacarbazine or temozolomide
- Carboplatin or cisplatin (ie, platinum agents)
- Antimetabolites
- Carmustine or lomustine (ie, nitrosoureas)
- Radiotherapy to volumes exposing the ovaries (evidence exists for risks but not for dose threshold)
- Radiotherapy to volumes exposing one versus two ovaries in the radiation field
- Haematopoietic stem-cell transplantation, independent of alkylating agents
- Unilateral oophorectomy
- Anthracyclines, bevacizumab, or novel agents (eg, tyrosine-kinase inhibitors or monoclonal antibodies)

Risks of hypogonadotropic hypogonadism after:

- Cranial radiotherapy
- Neurosurgical treatment for tumours in the hypothalamic–pituitary axis

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

Pregnancy outcomes and livebirths after:

- Oocyte and embryo cryopreservation
- Cryopreservation and transplantation of ovarian tissue
- Oophoropexy
- Hormonal suppression

Complications after:

- Oocyte and embryo cryopreservation
- Cryopreservation and transplantation of ovarian tissue
- Oophoropexy
- Hormonal suppression

Risk of premature ovarian insufficiency after:

- Cryopreservation of ovarian tissue
- Oophoropexy
- Hormonal suppression
- Immunomodulators (eg, AS101 or S1PR modulator)
- Oral contraceptive pill

Pregnancy outcomes and livebirths after:

- Oocyte donation

to female oncofertility and to enhance patients' and their families' quality of life.

Contributors

AF-G, RLM, EAHL, MMH, LBK, MDvdW, JL, WJET, and LCMK 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, LBK, JL, MDvdW, WJET, and LCMK drafted the manuscript; and HMvS, KCB, GPQ, EvD-dB, JB, RH, WHW, MMvdH-E, AA, RAA, AB, JDB, AMEB, ID, CD, NDI, HRH, RK, CL, TL, LRM, KR-W, CS, ES-G, WvD, MV, SV, EvdM, LSC, 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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