

Who should be informed about the potential infertility risk?

We strongly recommend that healthcare providers inform all CAYA cancer patients and their parents/caregivers/partners about the expected risk of infertility and/or early menopause, which may vary in magnitude based on the specific treatment planned (very low- to moderate-quality evidence).

Who should be counselled about fertility preservation?

We strongly recommend that healthcare providers¹ discuss fertility preservation options and alternative family planning with CAYA cancer patients and their parents/caregivers/partners if planned treatment will include alkylating agents² (high-quality evidence), radiotherapy to volumes exposing the ovaries (high-quality evidence), HSCT (very low-quality evidence), unilateral oophorectomy (very low-quality evidence), and/or cranial radiotherapy (very low-quality evidence).

If planned treatment will not include gonadotoxic modalities³, referral to a specialist to discuss fertility preservation options and family planning may be considered upon the request for additional information of the CAYA cancer patient and their parents/caregivers/partners (no studies).

What methods for reproductive preservation are appropriate to offer in counselling?⁴

Female CAYA cancer patients at potential risk of infertility: high-dose alkylating agents (CED ≥ 6000-8000 mg/m²), radiotherapy to volumes exposing the ovaries or HSCT

We strongly recommend offering oocyte or embryo cryopreservation to post-pubertal⁵ CAYA cancer patients in this treatment group only if cancer prognosis is not compromised by delay (existing guidelines).

We moderately recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal⁵ CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).⁶

We moderately recommend offering oophoropexy prior to radiotherapy to volumes exposing the ovaries to prepubertal and postpubertal⁵ CAYA cancer patients (very low-quality evidence).⁷

No recommendation can be formulated for offering hormone suppression during alkylating agent chemotherapy to postpubertal⁵ CAYA cancer patients in clinical care, but it could be offered in a research setting (inconclusive evidence).

Female CAYA cancer patients at potential risk of infertility: low-dose alkylating agents (CED < 6000-8000 mg/m²) or cranial radiotherapy

We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal⁵ CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment⁸ in the future (existing guidelines).⁹

We do not recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal⁵ CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).

No recommendation can be formulated for offering hormone suppression during alkylating agent chemotherapy to postpubertal⁵ CAYA cancer patients in clinical care, but it could be offered in a research setting (inconclusive evidence).

Female CAYA cancer patients at potential risk of infertility: unilateral oophorectomy

We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal⁴ CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment⁸ in the future (existing guidelines).⁹

No recommendation can be formulated for offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal⁵ CAYA cancer patients in this treatment group (insufficient evidence).

Female CAYA cancer patients not at risk of infertility: other treatments

We moderately recommend offering oocyte or embryo cryopreservation only to postpubertal⁴ CAYA cancer patients in this treatment group at high risk of cancer recurrence who may need gonadotoxic treatment⁸ in the future (existing guidelines).⁹

We do not recommend offering harvesting of ovarian tissue for cryopreservation to prepubertal and postpubertal⁵ CAYA cancer patients in this treatment group (very low-quality evidence, existing guidelines).

Abbreviations: CAYA, childhood, adolescent and young adult; HSCT, hematopoietic stem cell transplantation.

Note: Patients who will be treated with bilateral oophorectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations. The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

¹ The panel agreed that the choice of who should discuss fertility preservation and family planning options with the CAYA cancer patients and their families depends more on the provider's knowledge, patient's disease state and local access to fertility specialists than identifying a particular discipline to assume this role. Possibilities include paediatric oncologist, (paediatric) endocrinologist, fertility specialist, specialised nurse or other relevant healthcare provider. Of critical importance is that a system is in place to identify who is responsible for having the discussion.

² Alkylating agents: cyclophosphamide, procarbazine, busulfan, ifosfamide, mechlorethamine (nitrogen mustard), melphalan, chlorambucil, thiothepa, carmustin (BCNU), lomustine (CCNU), dacarbazine, temozolomide. A calculation formula for the cyclophosphamide equivalent dose can be found in Green et al. *Pediatr Blood Cancer*. 2014;61(1):53-67.

³ Therapies that do not include alkylating agents, radiotherapy to volumes exposing the ovaries, HSCT, unilateral oophorectomy, and/or cranial radiotherapy.

⁴ The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

⁵ Postpubertal status was defined as females with menarche.

⁶ The panel agreed that transplantation of post-pubertal cryopreserved ovarian tissue can be offered as clinical care, but advises careful evaluation of outcomes of the procedure as clinical research. Transplantation of pre-pubertal cryopreserved ovarian tissue can only be offered in the context of research due to the experimental nature. The panel recognizes the potential risk of reintroduction of malignant cells during auto-transplantation of ovarian tissue, especially for survivors of leukaemia, non-Hodgkin and metastasized solid tumours and the limited data of transplantation of pre-pubertal cryopreserved ovarian tissue.

⁷ Consultation with a radiation oncologist is needed to determine if oophoropexy is appropriate and to inform patients, caregivers or partners about the procedure's benefits and harms.

⁸ Patients needing high-dose alkylating agents ($\text{CED} \geq 6000\text{-}8000 \text{ mg/m}^2$), radiotherapy to volumes exposing the ovaries and/or HSCT in the future and if the procedure delay does not compromise patient outcome.

⁹ For patients not at risk of cancer recurrence, we do not recommend.

FIGURE: Recommendations for preservation of reproductive fertility for female patients with childhood, adolescent, and young adult cancer.

Female patients with CAYA cancer patients before age 25 years									
Strong recommendation ¹ to inform all patients with CAYA cancer and their parents, caregivers, and partners about the expected risk of infertility									
Counselling and methods for preservation of female reproductive fertility	At potential risk for infertility						Not at risk for infertility		
	High-dose alkylating agents ² , radiotherapy to ovaries, or HSCT		Low-dose alkylating agents ⁴ , or cranial radiotherapy		Unilateral oophorectomy		Other treatment groups ⁵		
	Postpubertal ³	Prepubertal	Postpubertal ³	Prepubertal	Postpubertal ³	Prepubertal	Postpubertal ³	Prepubertal	
Counselling about options for fertility preservation and alternative family planning	Strong recommendation ⁶	Strong recommendation ⁶	Strong recommendation ⁶	Strong recommendation ⁶	Strong recommendation ⁶	Strong recommendation ⁶	Moderate recommendation ⁷ only if requested	Moderate recommendation ⁷ only if requested	
Oocyte or embryo cryopreservation	Strong recommendation only if cancer prognosis is not compromised by delay ⁸		Moderate recommendation for only patients at high risk of cancer recurrence ^{8,9,10}		Moderate recommendation for only patients at high risk of cancer recurrence ^{8,9,10}		Moderate recommendation for only patients at high risk of cancer recurrence ^{8,9,10}		
Harvesting of ovarian tissue for cryopreservation ¹¹	Moderate recommendation ¹²	Moderate recommendation ¹²	Not recommended ¹²	Not recommended ¹²	No recommendation (insufficient evidence)	No recommendation (insufficient evidence)	Not recommended ¹²	Not recommended ¹²	
Oophorectomy (before radiotherapy to ovaries)	Moderate recommendation ^{13, 14}	Moderate recommendation ^{13, 14}							
Hormone suppression during alkylating agent chemotherapy	No recommendation for clinical care, only in research setting (insufficient evidence)		No recommendation for clinical care, only in research setting (insufficient evidence)						

Abbreviations: CAYA, childhood, adolescent, and young adult; HSCT, hematopoietic stem cell transplantation.

Notes: Patients who will be treated with bilateral oophorectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options as listed in the recommendations.

The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.

¹ This recommendation is based on very low- to moderate-quality evidence.

² High-dose alkylating agents defined as a cumulative alkylating agent dose (cyclophosphamide equivalent dose (CED)) at or above 6000-8000 mg/m²; A CED calculation can be found in Green et al. *Pediatr Blood Cancer*. 2014;61(1):53-67.

³ Post-pubertal status was defined as females with menarche.

⁴ Low-dose alkylating agents defined as a cumulative alkylating agent dose (cyclophosphamide equivalent dose (CED)) below 6000-8000 mg/m².

⁵ Therapies that do not include alkylating agents, radiotherapy to volumes exposing the ovaries, HSCT, unilateral oophorectomy, and/or cranial radiotherapy.

⁶ This recommendation is based on very low- to high-quality evidence.

⁷ This recommendation is based on expert opinions; no studies were identified.

⁸ This recommendation is based on evidence cited in high-quality existing evidence-based guidelines and expert opinions; no evidence in CAYA cancer patients was identified.

⁹ Patients who may need high-dose alkylating agents (CED ≥6000-8000 mg/m²), radiotherapy to volumes exposing the ovaries and/or HSCT in the future for cancer recurrence, and if prognosis will not be compromised by delay of treatment initiation.

¹⁰ For patients not at risk of cancer recurrence, we do not recommend.

¹¹ The panel agreed that transplantation of post-pubertal cryopreserved ovarian tissue can be offered as clinical care, but advises careful evaluation of outcomes of the procedure as clinical research. Transplantation of pre-pubertal cryopreserved ovarian tissue can only be offered in the context of research due to the experimental nature. The panel recognizes the potential risk of reintroduction of malignant cells during auto-transplantation of ovarian tissue, especially for survivors of leukaemia, non-Hodgkin and metastasized solid tumours and the limited data of transplantation of pre-pubertal cryopreserved ovarian tissue.

¹² This recommendation is based on a combination of very low-quality evidence, evidence cited in high-quality existing evidence-based guidelines and expert opinions.

¹³ Consultation with a radiation oncologist is needed to determine if oophorectomy is appropriate and to inform patients, caregivers or partners about the procedure's benefits and harms.

¹⁴ This recommendation is based on a combination of very low-quality evidence and expert opinions.

Publication

Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, Quinn GP, van Dulmen-den Broeder E, Byrne J, Haupt R, Wallace WH, van den Heuvel-Eibrink MM, Anazodo A, Anderson RA, Barnbrock A, Beck JD, Bos AME, Demeestere I, Denzer C, Di Iorgi N, Hoefgen HR, Kebudi R, Lambalk C, Langer T, Meacham LR, Rodriguez-Wallberg K, Stern C, Stutz-Grunder E, van Dorp W, Veening M, Veldkamp S, van der Meulen E, Constine LS, Kenney LB, van de Wetering MD, Kremer LCM, Levine J, Tissing WJE; PanCareLIFE Consortium. 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. *Lancet Oncol*. 2021;22(2):e45-e56.