Conclusions of evidence for fertility preservation in female patients with CAYA cancer

Who should be informed about potential risk of infertility?	
Satisfaction with information reported by patients diagnosed before age 25 years and their parents	**Quality of evidence**
Most patients (pre- and post-pubertal) are not satisfied with the content of fertility-related discussions with their (paediatric) oncology health healthcare providers, especially about information received on fertility risks, options to preserve fertility and alternative family planning	⊕⊕⊕⊖ MODERATE[1,2]
Desire for information reported by cancer patients diagnosed before age 25 years and their parents	**Quality of evidence**
Post-pubertal patients strongly desire information about the effects of cancer treatment on fertility (median score 9) and options for fertility preservation (median score 10) (scale 1-10, includes male and female)	⊕⊕⊖⊖ LOW[3]
Desire for information reported by healthcare providers of cancer patients diagnosed before 25 years	**Quality of evidence**
Some patients and their parents desire information about fertility preservation but paediatric oncologists report difficulties initiating discussions on this topic	⊕⊖⊖⊖ VERY LOW[4]
Who should be counselled about fertility preservation?	
Risk of premature ovarian insufficiency in female cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *alkylating agents* vs. no alkylating agents	⊕⊕⊕⊕ HIGH[5,6-14]
Increased risk after *increasing doses of alkylating agents*	⊕⊕⊕⊕ HIGH[5,6,7,9,11-14]
Increased risk after *cyclophosphamide* vs. no cyclophosphamide	⊕⊕⊕⊖ MODERATE[5,6-9,13]
Increased risk after *increasing doses of cyclophosphamide*	⊕⊕⊕⊖ MODERATE[6,7,9,13]
Increased risk after *procarbazine* vs. no procarbazine	⊕⊕⊕⊕ HIGH[5,9,11,13]
Increased risk after *increasing doses of procarbazine*	⊕⊕⊕⊕ HIGH[9,11,13]
Increased risk after *busulfan* vs. no busulfan	⊕⊕⊖⊖ LOW[8,10]
Unknown risk after *busulfan dose*	No studies
Increased risk after *melphalan* vs. no melphalan	⊕⊕⊖⊖ VERY LOW[9]
Unknown risk after *melphalan dose*	No studies
Unknown risk after chlorambucil, mechlorethamine, ifosfamide, thiotepa, carmustine (BCNU), lomustine (CCNU)	No studies
Unknown risk after *multiple alkylating agents and other chemotherapeutic agents* vs. single alkylating agents	No studies
Unknown risk after *antimetabolites*	No studies
Unknown risk after *platinum compounds*	No studies
Increased risk after *radiotherapy to volumes exposing the ovaries* vs. no radiotherapy	⊕⊕⊕⊕ HIGH[5,7-16]
Increased risk after *increasing doses of radiotherapy to volumes exposing the ovaries*	⊕⊕⊕⊕ HIGH[5,9,12-14]
Increased risk after *radiotherapy to volumes exposing the ovaries and alkylating agents* vs. either treatment in the same dose alone	⊕⊕⊕⊖ MODERATE[5,11,12]
Unknown risk in patients with *1* vs. *2 ovaries in the radiotherapy field*	No studies
Increased risk after *HSCT* vs. no HSCT independent of alkylating agents and/or radiotherapy to volumes exposing the ovaries	⊕⊖⊖⊖ VERY LOW[13]
Unknown risk after *autologous* vs. *allogeneic HSCT*	No studies

Unknown risk after *reduced conditioning vs. myeloablative conditioning* in HSCT survivors	No studies
Increased risk after *unilateral oophorectomy* vs. no unilateral oophorectomy	⊕⊖⊖⊖ LOW[9,13]
No significant effect of *oophoropexy* vs. no oophoropexy	⊕⊖⊖⊖ VERY LOW[12]
Increased risk after *older age at cancer treatment* vs. younger age	⊕⊕⊖⊖ LOW[5,7-10,12,13,15,16]
Unknown risk after *anthracyclines, high-dose etoposide, novel agents (monoclonal antibodies, tyrosine kinases inhibitors)*	No studies
Unknown risk in patients with a *genetic predisposition*	No studies
Risk of hypogonadotropic hypogonadism in female cancer survivors diagnosed before age 25 years	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no radiotherapy	⊕⊕⊖⊖ LOW[17]
Increased risk with *increasing doses of cranial radiotherapy*	⊕⊕⊕⊖ MODERATE[18]
Likelihood of pregnancy/live birth in female cancer survivors diagnosed before age 25 years	**Quality of evidence**
Decreased likelihood after *cyclophosphamide* vs. no cyclophosphamide	⊕⊕⊖⊖ LOW[19-21]
Decreased likelihood after *increasing doses of cyclophosphamide*	⊕⊕⊖⊖ LOW[19-21]
No significant effect of *ifosfamide* vs. no ifosfamide	⊕⊕⊖⊖ LOW[19]
No significant effect of *ifosfamide dose*	⊕⊕⊖⊖ LOW[19]
Decreased likelihood after *busulfan* vs. no busulfan	⊕⊕⊖⊖ LOW[19]
Decreased likelihood after *increasing doses of busulfan*	⊕⊕⊖⊖ LOW[19]
Decreased likelihood after *lomustine* vs. no lomustine	⊕⊕⊖⊖ LOW[19,20]
Decreased likelihood after *increasing doses of lomustine*	⊕⊕⊖⊖ LOW[19,20]
No significant effect of *procarbazine* vs. no procarbazine	⊕⊕⊕⊖ MODERATE[19-21]
No significant effect of *procarbazine dose*	⊕⊕⊕⊖ MODERATE[19-21]
No significant effect of *mechlorethamine* vs. no mechlorethamine	⊕⊕⊖⊖ LOW[20]
Decreased likelihood *after radiotherapy to volumes exposing the ovaries* vs. no radiotherapy	⊕⊕⊕⊖ MODERATE[20-22]
Decreased likelihood after *increasing doses of radiotherapy to volumes exposing the ovaries*	⊕⊕⊕⊖ MODERATE[20-22]
Decreased likelihood after *radiotherapy to the hypothalamic-pituitary axis* vs. no radiotherapy	⊕⊕⊖⊖ LOW[20,22]
No significant effect of *oophoropexy* vs. no oophoropexy	⊕⊕⊖⊖ LOW[20]
What methods for reproductive preservation are appropriate to offer in counselling?	
Live births after fertility preservation methods and timing in female cancer patients diagnosed before age 25 years	**Quality of evidence**
No studies investigating live births after *oocyte cryopreservation*	No studies
No studies investigating live births after *embryo cryopreservation*	No studies
No studies investigating live births after *in vitro maturation*	No studies
Live births reported after *transplantation of cryopreserved ovarian tissue* collected before cancer treatment (±45% success rate)	⊕⊖⊖⊖ VERY LOW[23-29]
At least 42 live births after *oophoropexy* before cancer treatment	⊕⊖⊖⊖ VERY LOW[14,30]
No significant difference between probability of a first pregnancy or live birth before age 40 between *oophoropexy* group vs. non-oophoropexy group	⊕⊖⊖⊖ VERY LOW[14]
Live births in patients treated with and without *GnRH analogues* during cancer treatment *(7 out of 7 pregnant patients with GnRH delivered 11 live births, 3 out of 3 pregnant patients without GnRH delivered 5 live births)*	⊕⊖⊖⊖ VERY LOW[31,32]
Live births after fertility preservation methods in female cancer patients	**Guideline**

(evidence cited in high-quality existing evidence-based guidelines)	
Likelihood of a pregnancy and live birth after IVF or ICSI using *vitrified oocytes* is not different from IVF or ICSI using fresh oocytes	*IKNL,[33] NCCN,[34] ASCO[35,36]*
Live births reported after *transplantation of cryopreserved ovarian tissue*	*IKNL,[33] ASCO[35,36] COSA,[37] COG,[38] ESMO[39]*
Pregnancies in females who underwent *oophoropexy* as young adolescents prior to Hodgkin lymphoma treatment	*COG[38]*
Restoration of ovarian function in female cancer patients diagnosed before age 25 years	**Quality of evidence**
Restoration of ovarian function after transplantation of cryopreserved ovarian tissue	⊕⊖⊖⊖ VERY LOW[29,40]
Risk of premature ovarian insufficiency in female cancer patients diagnosed before age 25 years	**Quality of evidence**
No significant effect of *oophoropexy* on the risk of premature ovarian insufficiency	⊕⊕⊖⊖ LOW[18]
Fewer patients had amenorrhea after *GnRH analogues* during cancer treatment compared to patients without GnRH analogues during cancer treatment	⊕⊖⊖⊖ VERY LOW[31]
Majority of females had regular menstrual cycles 1 to 17 years after end of alkylating agent chemotherapy and GnRH analogues	⊕⊖⊖⊖ VERY LOW[31,32]
No studies investigated effect after *immunomodulators AS101, S1P*	No studies
More patients had amenorrhea after *oral contraceptive pill* during chemotherapy compared to patients without oral contraceptive pill during chemotherapy	⊕⊖⊖⊖ VERY LOW[41]
Risk of premature ovarian insufficiency in female cancer patients *(evidence cited in high-quality existing evidence-based guidelines)*	**Guideline**
Endocrine function is restored after *re-implantation of ovarian tissue*	*COG[38]*
Ovarian function protected in adolescents who underwent oophoropexy prior to craniospinal radiation	*NCCN,[34] COG[38]*
Conflicting evidence about the efficacy of *GnRH analogues*	*IKNL,[33] NCCN,[34] ASCO[35,36] COSA,[37] COG,[38]* ESMO,[39] SIGN[42]
Inconclusive evidence about the efficacy of *oral contraceptives*	*IKNL,[33] NCCN[34]*
Complications after fertility preservation methods in female cancer patients diagnosed before age 25 years	**Quality of evidence**
Three female patients with intraoperative bleeding after *ovarian tissue cryopreservation*	⊕⊕⊖⊖ LOW[23,24,26,27,43-47]
In 12 females with leukaemia or non-Hodgkin lymphoma the *cryopreserved ovarian tissues* had tumour cell contamination	⊕⊖⊖⊖ VERY LOW[24,28,29,48]
No evidence of tumour contamination in *cryopreserved ovarian tissue* in females with non-metastasized solid tumours	⊕⊖⊖⊖ VERY LOW[23-25,29,43,44,49]
No evidence of tumour contamination in *cryopreserved ovarian tissue* in females with Hodgkin lymphoma	⊕⊖⊖⊖ VERY LOW[50]
No studies investigating patient-related complications after *oocyte or embryo cryopreservation, oophoropexy or hormone suppression*	No studies
No long-term complications reported after *GnRH analogues* during cancer treatment	⊕⊖⊖⊖ VERY LOW[32]
No studies investigating complications among offspring after *reproductive (preservation) methods*	No studies

No studies investigating perinatal complications after r*eproductive (preservation) methods* in patients treated with radiotherapy with volumes exposing the ovaries and/or uterus with or without oestrogen supplementation	No studies
Complications after fertility preservation methods in female cancer patients *(evidence cited in high-quality existing evidence-based guidelines)*	**Guideline**
No increased risk of *harms* among women with cancer undergoing *ovarian tissue, oocyte or embryo cryopreservation, or oophoropexy* as compared to the risk of harms among other women undergoing comparable procedures	*IKNL*[33]
Increased risks for a medically unwell patient undergoing IVF related to the anaesthetic and the oocyte collection procedure, such as haemorrhage, thrombosis and infection	*COSA*[37]
No increased risk of *congenital abnormalities among offspring* of women who underwent ICSI with *vitrified oocytes* as compared to offspring of women who underwent ICSI with oocytes after slow freezing, or ICSI or IVF with fresh oocytes	*IKNL*[33]
The evidence from children resulting from the replacement of the frozen embryos or fertilized frozen oocytes is reassuring	*COSA*[37]
No studies reporting cancer recurrence in humans; In one study 8 out of 26 *ovarian tissue samples* had leukaemia cells; In another study ovarian tissue from 24 Hodgkin lymphoma patients had no cancer cells	*COG*[38]
No pregnancy-related complications and congenital abnormalities among offspring of women who underwent *transplantation of cryopreserved ovarian tissue*	IKNL[39]
Any *laparoscopic technique* is associated with a small risk of complications, such as infection, bleeding and perforation of bowel, bladder or blood vessel	*COSA*[37]
No increased risk of congenital abnormalities among offspring of women who underwent *oophoropexy* and preserved their ovarian function	*IKNL*[33]
Adverse events associated with *GnRHa* are generally reversible and limited and include hot flashes, headaches, sweating, and vaginal dryness and when used for prolonged periods (>6 months) without add-back oestrogen treatment, there is a risk of bone depletion	*ASCO*[35,36] *IKNL,*[33] *COSA*[37]
Oocyte donation and surrogacy in female cancer survivors diagnosed before age 25 years	**Quality of evidence**
Live births after oocyte donation	⨁⊖⊖⊖ VERY LOW[51]
Pregnancy-related complications (premature delivery, placental haemorrhage with still born child, pre-eclampsia) after oocyte donation	⨁⨁⊖⊖ LOW[51,52]
Unknown pregnancy-related outcomes after surrogacy (using own eggs in gestational surrogate)	No studies

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