

Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group



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Female childhood, adolescent, and young adult cancer survivors have an increased risk of adverse pregnancy outcomes related to their cancer- or treatment-associated sequelae. Optimal care for childhood, adolescent, and young adult cancer survivors can be facilitated by clinical practice guidelines that identify specific adverse pregnancy outcomes and the clinical characteristics of at-risk subgroups. However, national guidelines are scarce and vary in content. Here, the International Late Effects of Childhood Cancer Guideline Harmonization Group offers recommendations for the counseling and surveillance of obstetrical risks of childhood, adolescent, and young adult survivors. A systematic literature search in MEDLINE database (through PubMed) to identify all available evidence published between January 1990 and December 2018. Published articles on pregnancy and perinatal or congenital risks in female cancer survivors were screened for eligibility. Study designs with a sample size larger than 40 pregnancies in childhood, adolescent, and young adult cancer survivors (diagnosed before the age of 25 years, not pregnant at that time) were eligible. This guideline from the International Late Effects of Childhood Cancer Guideline Harmonization Group systematically appraised the quality of available evidence for adverse obstetrical outcomes in childhood, adolescent, and young adult cancer survivors using Grading of Recommendations Assessment, Development, and Evaluation methodology and formulated recommendations to enhance evidence-based obstetrical care and preconception counseling of female childhood, adolescent, and young adult cancer survivors. Healthcare providers should discuss the risk of adverse obstetrical outcomes based on cancer treatment exposures with all female childhood, adolescent, and young adult cancer survivors of reproductive age, before conception. Healthcare providers should be aware that there is no evidence to support an increased risk of giving birth to a child with congenital anomalies (high-quality evidence). Survivors treated with radiotherapy to volumes exposing the uterus and their healthcare providers should be aware of the risk of adverse obstetrical outcomes such as miscarriage (moderate-quality evidence), premature birth (high-quality evidence), and low birthweight (high-quality evidence); therefore, high-risk obstetrical surveillance is recommended. Cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines and chest radiation. Female cancer survivors have increased risks of premature delivery and low birthweight associated with radiotherapy targeting the lower body and thereby exposing the uterus, which warrant high-risk pregnancy surveillance.

Key words: childhood cancer survivors, fecundity, late effects, pregnancy, prenatal care

Introduction

Five-year survival rates for childhood, adolescent, and young adult (CAYA) cancer patients now approach 80%.¹ Consequently, an increasing number of CAYA cancer survivors are at risk for adverse physical and psychosocial complications from their cancer or its treatment.² Reproductive health and

specifically pregnancy and delivery outcomes represent a critical area for long-term follow-up because having children is an important determinant of quality of life for CAYA cancer survivors.^{3–7}

Previous research indicates difficulty conceiving or carrying a pregnancy to term and increased risk of adverse pregnancy outcomes among CAYA

cancer survivors. For example, the risks of premature birth and postpartum hemorrhage are higher in CAYA cancer survivors than in women who did not have cancer,^{8–13} and these risks are further increased in survivors treated with abdominopelvic radiotherapy.^{9,11–14} Evidence-based clinical guidelines on surveillance in pregnancy can identify the

type and prevalence of specific obstetrical and perinatal complications, characterize the clinical features of those at risk, help survivors make informed decisions, facilitate counseling and timely referral to high-risk obstetrical care, and enable opportunities for interventions to optimize pregnancy outcomes.

Objective

Published clinical practice guidelines by North American and European cancer groups reference general obstetrical risks,^{15–18} but do not comprehensively assess the clinical features of those who could benefit from high-risk obstetrical follow-up. Herein, we summarize the results of a systematic review undertaken by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and present a critical appraisal of available evidence on obstetrical risks in CAYA cancer survivors, synthesizing these findings into evidence-based recommendations for

surveillance and counseling of CAYA cancer survivors during pregnancy and delivery owing to their cancer or cancer treatment.

Materials and Methods

This guideline focuses on facilitating timely identification of CAYA cancer survivors at high risk of obstetrical complications diagnosed as having cancer before the age of 25 years (and not pregnant at that time) who would benefit from preconception counseling and surveillance during pregnancy. Management of obstetrical complications is beyond the scope of the present guideline, which should defer to standards established by local or national health systems. Standardized definitions used in this guideline are presented in [Appendix 1](#).

The obstetrical guideline panel consisted of 33 experts from the United States of America, United Kingdom, Denmark, Germany, France, New Zea-

land, Australia, Japan, and the Netherlands from relevant disciplines, such as gynecology, obstetrics, midwifery, endocrinology, pediatric oncology, radiation oncology, epidemiology, and guideline methodology, and CAYA survivor or family representatives.

Methods of the IGHG have been described previously.¹⁹ For this guideline, concordances and discordances across existing survivorship guidelines of the North American Children's Oncology Group,¹⁵ the Dutch Childhood Oncology Group,¹⁶ the Scottish Intercollegiate Guidelines Network,¹⁸ and the UK Children's Cancer and Leukaemia Group¹⁷ were evaluated. We defined the major outcomes for obstetrical problems in survivors and congenital problems in offspring ([Appendix 1](#)). For all discordances and relevant outcomes, focused clinical questions were formulated to determine whether specific preconception consultation or surveillance was indicated. Four working groups evaluated

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Received Dec. 20, 2019; revised May 7, 2020; accepted May 29, 2020.

The authors report no conflict of interest.

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• <https://doi.org/10.1016/j.ajog.2020.05.058>



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the following topics: (1) adverse fetal outcomes in pregnancy (such as miscarriage), (2) adverse maternal outcomes in pregnancy, (3) delivery outcomes, and (4) congenital anomalies of the neonate.

A systematic literature search was performed in MEDLINE database (through PubMed) to identify all available evidence published between January 1990 and December 2018, using the search terms “childhood cancer,” “survivors,” “late effects,” and “obstetric problems.” Details of the full search strategy are included in [Appendix 2](#). All study designs with a sample size larger than 40 pregnancies in female childhood cancer survivors were eligible. To ensure rigorous review of manuscripts by at least 2 individuals, studies published in English were selected for analysis. All abstracts were screened by 2 independent reviewers (A.L.L.F.K. and 1 working group member). Disagreements were resolved through consensus. Cross-reference checking was performed to identify additional studies overlooked during the initial search. Relevant articles were summarized in 1 evidence table by 2 reviewers (A.L.L.F.K. and 1 working group member), such as a critical appraisal of risks of bias ([Appendix 3](#)). The evidence tables were subsequently assembled into summary of findings tables (A.L.L.F.K.) and revised where necessary (R.L.M. and L.C.M.K.). We assessed the quality of the body of evidence for each clinical question according to criteria based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE)²⁰ ([Appendix 4](#)). The quality of the total body of evidence is graded according to the following 4 levels: high (⊕⊕⊕⊕), further research is unlikely to change the confidence in the estimate of effect; moderate (⊕⊕⊕⊖), further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; low (⊕⊕⊖⊖), further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; and very low (⊕⊖⊖⊖), any estimate of effect is very uncertain. The level of

evidence decreased in the presence of study limitations (risk of bias in the studies), inconsistency of results between studies, indirectness of the study populations or outcomes, or imprecision of the effect estimates. The level of evidence increased if the effect sizes were large or there was evidence for a dose-response relationship.

Translating evidence into recommendations

Recommendations were drafted considering the level of the evidence, other effects of the expected risks (such as unnecessary medicalization), and the need for flexibility across healthcare systems.²¹ Terminology employed for radiotherapy and obstetrical outcomes can be found in [Appendix 5](#). Decisions were made through iterative group discussions; final recommendations represent unanimous consensus. The strength of the recommendations was graded according to published evidence-based methods ([Appendix 4](#)). Recommendations were classified into strong or moderate recommendations and based on high-quality evidence, moderate-quality evidence, or expert opinion.^{19,21,22} Pregnancy care-related recommendations from the IGHG cardiomyopathy guideline were adopted in this guideline to provide a complete overview of recommendations for pregnancy surveillance. The final harmonized recommendations were critically appraised by 4 independent external experts in the field and 2 survivor representatives.

Results

Discordances across existing long-term follow-up guidelines

Identification of concordances and discordances among existing surveillance recommendations is presented in [Appendix 6](#). The literature search yielded 2772 abstracts for pregnancy- and delivery-related risks and 2492 abstracts for congenital anomalies. In total, 98 full texts were reviewed, and 28 articles were included ([Figure](#), included articles in [Appendix 7](#)). The evidence tables and summary of findings are presented in [Appendix 8](#). The conclusions of evidence tables such as GRADE assessment are

summarized in [Table 1](#) and [Appendix 9](#) and depicted in a color scheme in [Appendix 10](#).

Who Needs Preconception Consultation or Specific Obstetrical Surveillance?

Evidence for risks during pregnancy

Miscarriage. There is moderate-level evidence that CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus are at increased risk of miscarriage compared with the general population.^{9,14,23–29} However, this association was only borderline significant in a large cohort from the British Childhood Cancer Survivor Study (BCCSS)²⁶ and not significant in 2 smaller studies.^{24,28} There is only low-level evidence for a dose-response relationship.^{29,30} The evidence indicated no significant effect owing to chemotherapy.^{9,26,30,31}

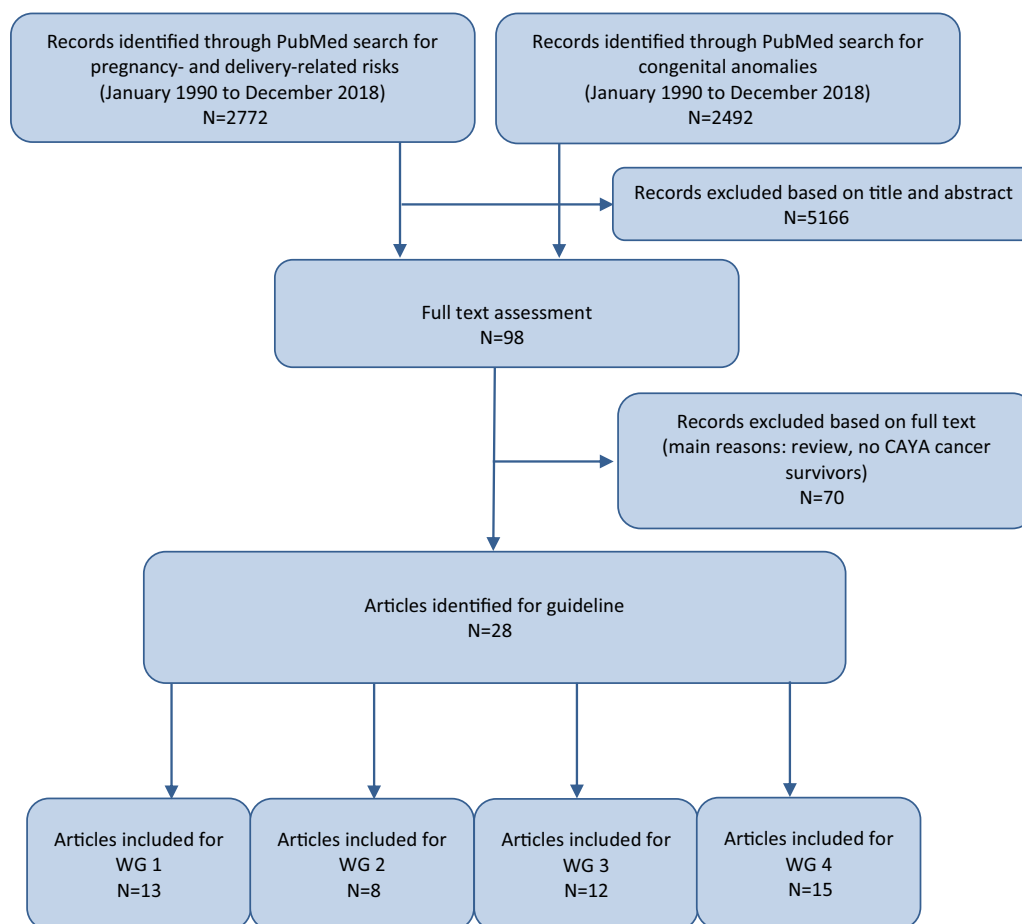
Termination of pregnancy. There is no data indicating an increased risk of medically induced terminations (very-low-level evidence)^{14,23,26,29,32} among CAYA cancer survivors in general. However, there is (very) low-level evidence for an increased risk for termination of pregnancy after any radiotherapy^{14,26} and chemotherapy.^{14,26} Of note, these findings are compromised by terminology in the relevant reports, which limits the distinction between medically indicated and elective termination of pregnancy.

Stillbirth. There is no data indicating an increased risk of stillbirth (moderate-level evidence) in CAYA cancer survivors in general^{9,29} and low-level evidence for increased risk of stillbirth after moderate to high doses of ovarian-uterine radiotherapy (>10 Gy)³³ or abdominopelvic radiotherapy (>25 Gy).³⁰

Gestational hypertension. There is very-low-level evidence for an effect of radiotherapy on the risk of gestational hypertension in CAYA cancer survivors compared with survivors treated without radiotherapy. The increased risk was only reported in the abdominopelvic irradiated survivors who had been

FIGURE

Flowchart of selected studies



Articles could be included for multiple working groups (WGs). Four working groups respectively evaluated the following topics: (1) adverse fetal outcomes in pregnancy (such as miscarriage), (2) adverse maternal outcomes in pregnancy, (3) delivery outcomes, and (4) congenital anomalies of the neonate.

CAYA, childhood, adolescent, and young adult; WG, working group.

van der Kooi. IGHG recommendations for management of obstetrical risks for female CAYA survivors. *Am J Obstet Gynecol* 2021.

diagnosed as having Wilms tumor in the BCCSS,³⁴ whereas 2 smaller studies did not find this association.^{13,35} A paper from the National Wilms Tumor Study Group observed an increased risk of any hypertensive disorder of pregnancy with increasing doses of flank radiotherapy, but because this was the only identified study assessing radiotherapy dose, the level of evidence is very low.

Preeclampsia. There is low-level evidence for an increased risk of preeclampsia in CAYA cancer survivors compared with controls, because this association was reported in 1 large population-based Australian study⁹ but

not in 2 other studies.^{11,13} Of note, 1 of these studies concerned a small sub-cohort of 6 CAYA cancer survivors exposed to radiotherapy to the abdomen, none of whom developed preeclampsia.¹³ No studies were identified that evaluated the risk of preeclampsia after chemotherapy.

Maternal anemia. There is low-level evidence that abdominopelvic radiotherapy increases the risk of maternal anemia in CAYA cancer survivors compared with nonirradiated survivors. This is based on increased risks observed in 1 large study,³⁴ whereas the effect was not observed in another equally sized cohort.¹¹

Gestational diabetes. There is low-level evidence overall for an increased risk of gestational diabetes in CAYA cancer survivors compared with controls, based on 1 report that found the association⁹ and 2 that did not find an association.^{11,35} There is low-level evidence for an effect of abdominopelvic radiotherapy,^{9,11,34,35} moderate-level evidence that there is no effect of chemotherapy,^{9,11,35} and high-level evidence that there is no effect of age at diagnosis^{9,11,34} on the risk of gestational diabetes.

Malposition of the fetus. There is no increased risk of malposition of the fetus

TABLE 1

Overall conclusions of evidence for obstetrical risks in female childhood and adolescent cancer survivors (key outcomes)**Who needs preconception counseling? Who needs high-risk pregnancy surveillance?**

Risk of miscarriage in female cancer survivors diagnosed before the age of 25 years	Level of evidence ^a
No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{9,24,25,27,29,32}
Increased risk after (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊖ Moderate ^{9,14,23–29}
Increased risk with increasing doses of abdominopelvic and pituitary radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{29,30}
No significant effect of chemotherapy vs no chemotherapy	⊕ ⊕ ⊕ ⊖ Moderate ^{9,14,25,26,30}
Increased risk after chemotherapy and radiotherapy (no specific field) vs no chemotherapy and radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{9,14,24,25,30}
No significant effect of age at diagnosis	⊕ ⊕ ⊖ ⊖ Low ⁹
Risk of terminations in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ^{29,32}
Increased risk after radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{14,26}
Increased risk after chemotherapy vs no chemotherapy	⊕ ⊖ ⊖ ⊖ Very low ^{14,26}
Increased risk after chemotherapy or radiotherapy (to any field or gonadal) vs no chemotherapy and radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{14,23}
Risk of stillbirth in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{9,29}
No significant effect of radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{9,14,26,30,41}
Increased risk after high-dose ovarian-abdominal radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{30,33,41}
Increased risk after abdominopelvic radiotherapy (>1.00 Gy) given before menarche vs no radiotherapy, but no significant effect when given after menarche	⊕ ⊕ ⊖ ⊖ Low ³³
No significant effect of chemotherapy vs no chemotherapy	⊕ ⊕ ⊖ ⊖ Low ^{9,14,26,30}
No significant effect of alkylating agent dose	⊕ ⊕ ⊖ ⊖ Low ³³
No significant effect of alkylating agents in combination with abdominal-pelvic radiation vs no alkylating agents and abdominal-pelvic radiation	⊕ ⊕ ⊖ ⊖ Low ^{14,23,30}
Risk of gestational hypertension in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ^{13,35}
Increased risk after abdominopelvic radiotherapy vs no radiotherapy	⊕ ⊖ ⊖ ⊖ Very low ^{13,34,35}
Increased risk with increasing doses of flank radiotherapy in CAYA Wilms tumor survivors	⊕ ⊖ ⊖ ⊖ Very low ⁴⁵
No significant effect of chemotherapy vs no chemotherapy.	⊕ ⊖ ⊖ ⊖ Very low ³⁵
No significant effect of age at diagnosis	⊕ ⊕ ⊖ ⊖ Low ³⁴
Risk of preeclampsia in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{9,11,13}
No significant effect of abdominopelvic radiotherapy vs no radiotherapy	⊕ ⊖ ⊖ ⊖ Very low ¹³
Risk of maternal anemia in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{9,11}
Increased risk after (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{11,34}
Increased risk after chemotherapy vs no chemotherapy	⊕ ⊕ ⊖ ⊖ Low ¹¹

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(continued)

TABLE 1**Overall conclusions of evidence for obstetrical risks in female childhood and adolescent cancer survivors (key outcomes)** (continued)**Who needs preconception counseling? Who needs high-risk pregnancy surveillance?**

No significant effect of radiotherapy and chemotherapy vs controls	⊕ ⊕ ⊖ ⊖ Low ¹¹
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊖ Moderate ^{11,34}
Risk of gestational diabetes in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{9,11,35}
Increased risk after (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{9,11,34,35}
No significant effect of chemotherapy vs no chemotherapy	⊕ ⊕ ⊕ ⊖ Moderate ^{9,11,35}
Increased risk after chemotherapy in combination with radiotherapy vs controls	⊕ ⊖ ⊖ ⊖ Very low ^{9,11}
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊕ High ^{9,11,34}
Risk of malposition in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ¹⁰
No significant effect of radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊖ Low ³⁴
Increased risk with increasing doses flank radiation	⊕ ⊖ ⊖ ⊖ Very low ⁴⁵
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊕ High ^{10,34}
Risk of postpartum hemorrhage in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{8–10,13,34}
Increased risk after abdominopelvic radiotherapy vs no radiotherapy	⊕ ⊖ ⊖ ⊖ Very low ^{13,34}
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊖ Low ³⁴
Risk of premature birth in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{9–13,27,35}
Increased risk after (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊕ High ^{9,11,13,28,34,35}
Increased risk with increasing doses of ovarian-abdominal radiotherapy (>5/15 Gy)	⊕ ⊕ ⊕ ⊖ Low ^{12,45}
Increased risk after chemotherapy vs no chemotherapy	⊕ ⊕ ⊕ ⊖ Low ^{9,11,35}
No significant effect of alkylating agent dose	⊕ ⊕ ⊖ ⊖ Low ¹²
Increased risk after radiotherapy and chemotherapy vs no radiotherapy and chemotherapy	⊕ ⊕ ⊕ ⊖ Moderate ^{9,11}
Increased risk in survivors aged >5 years at cancer diagnosis vs controls, but no significant effect in survivors aged <5 years at cancer diagnosis	⊕ ⊕ ⊖ ⊖ Low ^{9,11,34}
Risk of low birthweight in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{9–13,27,35}
Increased risk after (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊕ High ^{9,11,13,28,30,34,35}
Increased risk after increasing doses of abdominopelvic radiotherapy (>2.5/25 Gy)	⊕ ⊕ ⊕ ⊖ Moderate ^{12,27,30,45}
Increased risk after chemotherapy vs no chemotherapy	⊕ ⊖ ⊖ ⊖ Very low ^{9,11,30,35}
No significant effect alkylating agent dose	⊕ ⊖ ⊖ ⊖ Very low ¹²
Increased risk after radiotherapy and chemotherapy vs no radiotherapy and chemotherapy	⊕ ⊖ ⊖ ⊖ Very low ^{9,11,30}
Increased risk in survivors aged ≥20 years at cancer diagnosis vs controls, but no significant effect in survivors aged <20 years at cancer diagnosis	⊕ ⊖ ⊖ ⊖ Very low ^{9,11,34}
Risk of delivery of a child small for gestational age in female cancer survivors diagnosed before the age of 25 years	Level of evidence

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(continued)

TABLE 1**Overall conclusions of evidence for obstetrical risks in female childhood and adolescent cancer survivors (key outcomes)** (continued)**Who needs preconception counseling? Who needs high-risk pregnancy surveillance?**

No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{11,12,35}
No significant effect of (abdominopelvic) radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{13,28,30,35}
Increased risk after increasing doses of abdominopelvic radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{12,30}
No significant effect of chemotherapy vs no chemotherapy.	⊕ ⊖ ⊖ ⊖ Very low ³⁵
No significant effect of alkylating agent dose	⊕ ⊕ ⊖ ⊖ Low ¹²
No significant effect of radiotherapy and chemotherapy vs surgery only	⊕ ⊖ ⊖ ⊖ Very low ³⁰
Risk of intrauterine growth restriction in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ⁹
Likelihood of vaginal delivery in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Decreased likelihood of vaginal birth in in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊕ High ^{8,10}
Likelihood of assisted vaginal delivery in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased likelihood of in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{8,10,13}
No significant effect of radiotherapy vs no radiotherapy	⊕ ⊖ ⊖ ⊖ Very low ¹³
No significant effect of age at diagnosis	⊕ ⊕ ⊖ ⊖ Low ¹⁰
Risk of any cesarean delivery in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased likelihood of any cesarean delivery in in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{9–11,35}
Increased likelihood after radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ^{9,35}
Increased likelihood after chemotherapy vs no chemotherapy,	⊕ ⊕ ⊖ ⊖ Low ^{9,35}
Significant effect of age at diagnosis (increased effect if 0–14 years at diagnosis)	⊕ ⊖ ⊖ ⊖ Very low ^{9,10}
Likelihood of an elective or primary cesarean delivery in female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased likelihood in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊕ High ^{8,10,11,34}
Increased likelihood after radiotherapy vs no radiotherapy, specifically after abdominal radiotherapy in Wilms survivors	⊕ ⊕ ⊕ ⊖ Moderate ³⁴
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊕ High ³⁴
Likelihood of an emergency/secondary/urgent cesarean delivery in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased likelihood in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊖ Moderate ^{8,10,13,34}
No significant effect of radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊕ High ^{13,34}
No significant effect of age at diagnosis	⊕ ⊕ ⊕ ⊖ Moderate ^{8,34}
Risk of congenital anomalies or abnormalities in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊕ ⊕ High ^{9,11,13,32,36–40}
No significant effect of (ovarian-abdominal) radiotherapy vs no radiotherapy	⊕ ⊕ ⊕ ⊕ High ^{13,30,36,38,39,41,42}
No significant effect of radiotherapy dose	⊕ ⊕ ⊕ ⊖ Moderate ^{30,36,41,42,45}
No significant effect of alkylating agents vs no alkylating agents	⊕ ⊕ ⊕ ⊖ Moderate ^{30,38,39,41,42,52}
No significant effect of alkylating agent dose	⊕ ⊖ ⊖ ⊖ Very low ⁴²

van der Kooi. IGHG recommendations for management of obstetrical risks for female CAYA survivors. Am J Obstet Gynecol 2021.

(continued)

TABLE 1**Overall conclusions of evidence for obstetrical risks in female childhood and adolescent cancer survivors (key outcomes)** (continued)**Who needs preconception counseling? Who needs high-risk pregnancy surveillance?**

No significant effect of alkylating agents in combination with abdominal-pelvic radiation vs no alkylating agents and abdominal-pelvic radiation	⊕ ⊕ ⊕ ⊖ Moderate ^{23,30,41}
No significant effect of age at diagnosis	⊕ ⊖ ⊖ ⊖ Very low ³⁹
Rate of supervision of high-risk pregnancy in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased rates in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ³⁴
No significant effect of radiotherapy vs no radiotherapy	⊕ ⊕ ⊖ ⊖ Low ³⁴
Risk of retained placenta/manual removal of the placenta in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊕ ⊖ ⊖ Low ^{9,13}
Risk of placental pathologies in female cancer survivors diagnosed before the age of 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ¹⁰
Risk of resuscitation of the neonate born to female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ⁹
Likelihood of admission to a special care unit in neonates born to female cancer survivors diagnosed before the age of 25 years	Level of evidence
Increased likelihood in CAYA cancer survivors vs controls	⊕ ⊖ ⊖ ⊖ Very low ⁹

CAYA, childhood, adolescent, and young adult.

^a Citations refer to papers on which the GRADE level of evidence was based on and do not necessarily support the overall conclusion.van der Kooi. IGHG recommendations for management of obstetrical risks for female CAYA survivors. *Am J Obstet Gynecol* 2021.

(low-level evidence) and no effect of radiotherapy on this outcome (very—low-level evidence).^{10,34}

Evidence for gestational length and birthweight

Premature birth. CAYA cancer survivors are at increased risk of premature birth (before 37 weeks' gestation) compared with siblings and the general population (moderate-level evidence).^{9–13,27,28,35} High-level evidence indicated that radiotherapy to volumes exposing the uterus increases the risk of premature birth.^{9,11,13,28,34,35} Although 2 reports did not delineate specific radiotherapy volumes, categorizing groups only as treated with or without any type of radiotherapy, but both also indicated increased risk after treatment with radiotherapy.^{9,11} We found low-level evidence for a dose-response relationship with radiotherapy, including 1 study

that found a trend for increasing risk with increasing flank radiation dose, specifically with doses >15 Gy.¹⁴ Another study reported increased risks specifically with doses >5 Gy to the uterus and, in a smaller subcohort treated before menarche, an even lower threshold of 2.5 Gy.¹² One study reported that chemotherapy was associated with an increased risk of premature birth (low-level evidence).¹¹ However, this effect was not found in a small Japanese study³⁵ or in a large Australian population-based study.⁹ One study did not observe a significant effect of alkylating agent dose on the risk of premature birth (very—low-level evidence).¹²

Low birthweight. There is moderate-level evidence for an increased risk of low birthweight (below 2500 grams) delivery in CAYA cancer survivors compared with controls^{9–13,27,35} and high-level

evidence for this outcome after radiotherapy to volumes exposing the uterus.^{9,11,13,28,30,34,35} A dose-response relationship was observed in survivors of Wilms tumor³¹ and risk of an effect of radiotherapy was observed after >2.5 Gy¹² to the uterus and >25 Gy³⁰ abdominopelvic radiotherapy (moderate-level evidence).^{12,30} Although 3 studies did not identify chemotherapy as a risk factor for low birthweight,^{9,30,35} the association was suggested in 1 report¹¹ (very-low-level evidence). There also seems to be no effect of alkylating agent dose (very-low-level evidence) on the risk of giving birth to a child with a low birthweight.¹²

Small for gestational age. There is low-level evidence for no increased risk of small for gestational age (<10th percentile birthweight for gestational age) delivery among CAYA cancer

survivors in general compared with controls.^{11,12,35} Although radiotherapy vs no radiotherapy was not found to be significantly associated with this outcome in 4 studies,^{13,28,30,35} 2 studies reported that patients treated with specific doses of abdominopelvic radiotherapy (>5 Gy and >25 Gy, respectively) had an increased risk (low-level evidence) of small for gestational age delivery.^{12,30}

Evidence for mode of delivery

Vaginal delivery. There is high-level evidence indicating that rates of spontaneous vaginal births are lower in CAYA cancer survivors than in controls.^{8,10} There was no significant difference between survivors and controls (moderate-level evidence)^{8,10,13} and no significant effect of radiotherapy (very-low-level evidence)¹³ on occurrence of assisted vaginal delivery.

Cesarean delivery. There is low-level evidence for higher rates of “any cesarean section” (data from reports that did not distinguish between elective [primary] and emergency [secondary or urgent] cesarean deliveries) among CAYA cancer survivors compared with controls,^{9–11,35} including reports evaluating prevalence after radiotherapy and chemotherapy (low-level evidence).^{9,35}

High-level evidence was identified for an increased rate of an elective cesarean delivery,^{8,10,11,34} especially after abdominopelvic radiotherapy (moderate-level evidence).³⁴ No significantly increased rate was observed for the occurrence of emergency cesarean delivery (moderate-level evidence).^{8,10,13,34} Radiotherapy and age at diagnosis did not significantly affect the rate of emergency cesarean delivery (high-level evidence).^{8,13,34}

Evidence for risks related to delivery

Postpartum hemorrhage. There is low-level evidence for an increased risk of postpartum hemorrhage in CAYA cancer survivors compared with controls. An increased risk was observed in 1 report⁸ but not in 4 others.^{9,10,13,34} There is low-level evidence for a statistically significant effect of abdominal

radiotherapy for this outcome based on 1 small study suggesting an increased risk,¹³ whereas another larger study did not find an increased risk.³⁴

Evidence for problems of the neonate

Congenital anomalies. There is high-level evidence that there is no increased risk of congenital anomalies among neonates of CAYA cancer survivors compared with controls. A total of 9 studies, with large heterogeneity in outcome definitions, have reported on the prevalence of congenital anomalies and none reported an increased risk.^{9,11,13,32,36–40} There is also high-level evidence that there is no significant effect of radiotherapy delivered as part of CAYA cancer therapy on the risk of congenital anomalies.^{13,30,36,38,39,41,42}

Evidence for additional obstetrical outcomes

The evidence levels on the risk of retained placenta or manual removal of the placenta, placental pathologies, fetal growth restriction, uterine scar from previous surgery, and perineal laceration or rupture were low to very low or revealed no increased risk for these outcomes. Concerning the neonate, the evidence levels on the risk of resuscitation and admission to a special care unit were very low. Additional outcomes evaluated in a limited number of papers are reported in [Appendix 6](#), also indicating only low to very low levels of evidence.

Translating evidence into recommendations

Final recommendations, formulated based on at least moderate or high levels of evidence for the risk of obstetrical outcomes and its determinants ([Table 1](#)), are presented in [Table 2](#). There was moderate-level evidence for an increased risk of miscarriage after radiotherapy to volumes exposing the uterus, and high-level evidence for an increased risk of premature birth (<37 weeks' gestation) and low birthweight (<2500 grams) after radiotherapy to volumes exposing the uterus. In addition, CAYA cancer survivors had higher rates of elective cesarean delivery (high-level evidence). There was

high-level evidence that there is no increased risk of congenital anomalies in the offspring of CAYA cancer survivors. Lower levels of evidence were included for the identification of gaps in knowledge and future research directions (Panel). Radiotherapy was of specific interest if and when a dose-response relationship was identified. Although low-level evidence suggests a dose-response relationship of radiotherapy to volumes exposing the uterus with the risk of miscarriage,^{29,30} insufficient evidence is available to identify a safe threshold dose.

For every adverse outcome, the balance between benefits and harms of preconception counseling and surveillance, resource use, acceptability to stakeholders, and feasibility or barriers for implementation was considered. The panel agreed that, in general, all female CAYA cancer survivors of reproductive age should be informed by healthcare providers about their potential risk for adverse obstetrical outcomes based on cancer treatment exposures (strong recommendation).

For example, female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their healthcare providers should be aware of the risk of adverse obstetrical outcomes such as miscarriage (moderate-quality evidence), premature birth (high-quality evidence), and low birthweight (high-quality evidence). In addition, high-risk obstetrical surveillance is recommended for this patient group (strong recommendations). The panel agreed that the benefits of preconception counseling and obstetrical surveillance for these outcomes (ie, early detection of fetal growth restriction or threatened premature delivery requiring intervention to ensure optimal neonatal outcome) clearly outweigh the potential harms (eg, stress, anxiety, and potential higher healthcare costs).

Regarding the increased likelihood of elective cesarean delivery, the panel agreed that no recommendations could be drawn because this risk may be attributable to myriad factors such as the survivor's or the healthcare provider's concern.

TABLE 2

Harmonized recommendations for counseling and surveillance in pregnancy**General recommendation**

Healthcare providers should discuss the risk of adverse obstetrical outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age.

Who needs preconception counseling?

Female CAYA cancer survivors and their healthcare providers should be aware that there is no evidence to support that survivors have an increased risk of giving birth to a child with congenital anomalies (high-quality evidence).

Female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their healthcare providers should be aware of the risk of adverse obstetrical outcomes such as miscarriage (moderate-quality evidence), premature birth (high-quality evidence), and low birthweight (high-quality evidence).

Who needs specific obstetrical surveillance during pregnancy?

High-risk obstetrical surveillance is recommended for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus owing to the risk of premature birth and low birthweight (high-quality evidence).

Who needs specific cardiac surveillance during pregnancy? (based on IGHG cardiomyopathy guideline⁴³)

Cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines and chest radiation (moderate-level recommendation, moderate-quality evidence).⁴³

No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately before or during the first trimester of pregnancy (moderate-level recommendation, low-quality evidence).⁴³

CAYA, childhood, adolescent, and young adult; IGHG, International Late Effects of Childhood Cancer Guideline Harmonization Group.

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The absence of an increased risk of congenital anomalies (high-quality evidence) is of great importance to survivors and the panel agreed that female CAYA cancer survivors and their healthcare providers should be aware of this (strong recommendation).

Based on previous recommendations from the IGHG for cardiomyopathy surveillance for CAYA cancer survivors, cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines and chest radiation (moderate recommendation).⁴³ No recommendations have been formulated for the frequency of ongoing cardiomyopathy surveillance in pregnant survivors who have normal left ventricular systolic function immediately before or during the first trimester of pregnancy. However, the IGHG panel recommended that healthcare providers remain alert for cardiomyopathy in survivors treated with anthracyclines and chest-directed radiation who present with commonly reported symptoms such as shortness of breath, fatigue, and ankle swelling.⁴³ In addition, the panel emphasized that

CAYA cancer survivors with compromised left ventricular systolic function (<30%) before pregnancy are more likely to have further reduction in cardiac function during pregnancy or postpartum period, irrespective of lifetime anthracycline dose.⁴³

Comments

This paper presents the IGHG recommendations for counseling and surveillance of female CAYA cancer survivors before and during pregnancy. Evidence-based recommendations for survivor risk groups were formulated to facilitate consistent long-term follow-up care, optimize the quality of care, and minimize burden of disease and unnecessary surveillance. Because of this effort, the guideline panel also stressed the need for future research in larger cohorts to advance understanding about the radiotherapy dose-response relationship to adverse obstetrical outcomes.

Critical evaluation of the published literature aided by the GRADE methodology yielded moderate-level evidence that CAYA cancer survivors are at increased risk of miscarriage after radiotherapy.^{9,23,24,26,28,29,31} When

reported, the definition of a miscarriage was heterogeneous (usually pregnancies ending before 20 weeks' gestation or, in the BCCSS, before 24 weeks' gestation) and the panel acknowledged the potential for reporting bias in both self-reported and registry-based data. However, increased risks were observed in 3 large cohorts, from the North American Childhood Cancer Survivor Study (self-reported miscarriage, not further specified¹⁴), Australia (registered threatened miscarriage after 20 weeks' gestation⁹), and Denmark (registered spontaneous abortion, not further specified²⁹). Although low-level evidence suggests a dose-response relationship with radiotherapy to volumes exposing the uterus,^{29,30} there is insufficient evidence to identify a safe threshold dose. Even though there is no specific action to reduce this risk, the panel agreed survivors need to be counseled of their potential increased risk of miscarriage.

Lack of definition of termination of pregnancy^{14,29,32} and broad and overlapping definitions of stillbirth (eg, the fetus not surviving after 20 weeks'

gestation,⁹ after 28 weeks' gestation,²⁹ or combined with neonatal deaths within the first 28 days of life³³), and potential reporting bias resulted in a low body of evidence on which to base recommendations (Panel).

Interestingly, a recent study in survivors aged 39 years or less at cancer diagnosis with strong outcome reporting found a significantly reduced risk of termination of pregnancy,⁴⁴ stressing the need for further research to define more accurately the prevalence of this outcome.

We identified high-level evidence for the increased risks of premature birth and low birthweight after radiotherapy to volumes exposing the uterus.^{9–14,27,28,30,31,34,35} The evidence for dose-response relationships between radiotherapy and miscarriage, premature birth, and low birthweight is compelling, but clear evidence to determine a safe threshold dose is lacking. Different approaches have been used to assess radiotherapy dose, giving rise to bias when comparing these studies.^{12,27,29,30,45} In modern clinical practice, approximation of organ-specific radiation exposure parameters that are much closer to the individual true dose distribution during treatment is feasible and expected to facilitate a more accurate assessment of the relationship of radiation dose and obstetrical risks in future studies.

Radiotherapy to volumes exposing the ovaries, that is, radiotherapy targeting the lower body and thereby exposing the ovaries to substantial amounts of ionizing radiation, is associated with premature ovarian insufficiency^{46–49} but does not lead to increased risk of stillbirth or congenital anomalies compared with the general population. Mechanisms leading to increased rates of miscarriage, premature delivery, and low birthweight have not been completely elucidated, but several hypotheses have been proposed. Radiotherapy to volumes exposing the uterus can damage the uterine vasculature and muscular development⁵⁰ and potentially impair endometrial function because of impaired blood supply. This may result in poor implantation of the embryo and

poor placental growth which could contribute to subsequent early miscarriage. The increased risks of premature birth and low birthweight may result from uterine vasculature injury leading to impaired uteroplacental blood flow, insufficient placental development, and hence fetal growth restriction or may result from a reduced uterine elasticity and volume.^{50,51} In addition, hormonal deficiency as a consequence of ovarian failure may lead to smaller uterine volumes.⁵¹

Cancer survivors should be counseled about obstetrical risks when developmentally and clinically appropriate. Multimorbidity is often the norm in CAYA cancer survivors, emphasizing the need to understand specific treatment-related risks and how collectively these conditions may affect the course of pregnancy. Communication among obstetrical and oncology providers and survivors is key in these complicated cases. Preconception consultation and obstetrical surveillance may lead to referral to a specialized obstetrical team rather than a general obstetrical or midwifery team and ensure selection of a hospital for the place of birth rather than a birth center or home. Further clinical management, such as antenatal monitoring for heightened risk of low birthweight or cardiac monitoring, should adhere to established obstetrical care guidelines.

No recommendations were formulated based on the high level of evidence concerning the increased likelihood of an elective cesarean delivery. The increased obstetrical risks of cancer survivors may influence the varied clinical, cultural, and personal factors for patients and providers that contribute to decision making about elective cesarean deliveries. Reassuringly, the likelihood of an emergency cesarean delivery was not increased among women treated with radiotherapy.

A large and consistent body of evidence indicates that neonates of CAYA cancer survivors treated with and without radiotherapy are not at increased risk of congenital anomalies.^{13,30,36,38,39,41,42} Because this is often a major concern in CAYA cancer

survivors, the panel recommends reassurance of CAYA cancer survivors that there is no indication of such an increased risk.

The recommendations presented here have benefited from the systematic appraisal of bias and transparent implementation of GRADE in assessing the available evidence. Their relevance is further strengthened by the careful considerations that the multidisciplinary and international panel made by extrapolating evidence to recommendations. Some limitations include variability of definitions of outcomes and availability of specific details regarding radiotherapy (dose and site) and chemotherapy (agents and dose) across studies, potential study biases without indication of response rates, and the scarcity of studies with multivariable analyses to address confounding clinical issues. In addition, the body of evidence often indicated no increased risk, but few power calculations were presented in the papers to distinguish between absence of evidence and evidence of absence of an association. We note that we have not addressed thyroid dysfunction in CAYA cancer survivors, which is an important topic because latent hypothyroidism can affect fetal brain development.^{15,16} Recommendations on surveillance will be formulated in an upcoming IGHG guideline on surveillance of thyroid dysfunction. A periodic update of the obstetrical recommendations is planned, and the IGHG thyroid dysfunction surveillance recommendations will then also be included.

The identification of key gaps in knowledge is an important result of the harmonization process (Panel). These evidence gaps should be addressed in strong methodical and comprehensive studies from sufficiently large cohorts or preferably international multicenter collaborative projects to increase generalizability of the results.

Conclusion

This IGHG analysis identified specific adverse obstetrical related outcomes that are increased in CAYA cancer survivors to characterize the population that will benefit specifically from an

individualized preconception consultation and pregnancy surveillance. Key findings are that there are increased risks of premature delivery and low birth-weight associated with radiotherapy targeting the lower body and thereby exposing the uterus, which warrant high-risk pregnancy surveillance, and that survivors should be reassured that there is no increased risk of congenital abnormality. ■

ACKNOWLEDGMENTS

We thank the following people for critically appraising the recommendations and the manuscript: Melanie Davies, Michael Hawkins, Ann Partridge, and Lisa Webber (expert panel) and Eline van der Meulen and Katie Weyer (patient advocates).

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