Recommendations for counseling and surveillance of obstetric risks for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Anne-Lotte L.F. van der Kooi, Renee L. Mulder, Melissa M. Hudson, Leontien C. M. Kremer, Rod Skinner, Louis S. Constine, Wendy van Dorp, Eline van Dulmen-den Broeder, Jeanette Falck Winther, W. Hamish Wallace, Jason Waugh, Teresa Woodruff, Richard A Anderson, Saro H. Armenian, Kitty Bloemenkamp, Hilary Critchley, Charlotte Demoor-Goldschmidt, Matthew J. Ehrhardt, Daniel M. Green, William A. Grobman, Yuriko Iwahata, Iris Krishna, Joop Laven, Gill Levitt, Lillian R. Meacham, Emily S. Miller, Annemarie Mulders, Angela Polanco, Cécile M. Ronckers, Amber Samuel, Tom Walwyn and Jennifer Levine*, Marry M. van den Heuvel-Eibrink*

**Equally contributed*

Submitted

ABSTRACT

Female survivors of childhood, adolescent, and young adult (CAYA) cancer have an increased risk of adverse pregnancy outcomes (e.g. miscarriage, premature delivery, perinatal cardiomyopathy) related to their cancer or treatment-associated sequelae. Optimal care for CAYA cancer survivors can be facilitated by clinical practice guidelines that identify specific adverse pregnancy outcomes and the clinical characteristics of at-risk subgroups that should be closely monitored. However, national guidelines are scarce and vary considerably in their recommendations. Thus, this guideline from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) evaluated the quality of available evidence for adverse obstetric outcomes in CAYA cancer survivors (diagnosed before 25 years of age and not pregnant at that time), and formulated recommendations to enhance evidence-based obstetric care and counseling of female CAYA cancer survivors. We recommend that healthcare providers should discuss the risk of adverse obstetric outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age. Survivors and their health care providers should be aware that there is no evidence to support that there is 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 health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence) and therefore, high risk obstetric surveillance is recommended. Based on the IGHG cardiomyopathy guideline, cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation. Gaps in knowledge and directions for future research are presented to further refine evidence-based recommendations.

INTRODUCTION

Advances in cancer treatment strategies have resulted in 5-year survival for childhood, adolescent, and young adult (CAYA) cancer patients that approaches 80%[1]. Consequently, increasing numbers of CAYA cancer survivors are at risk for adverse cancer and/or treatment-related complications that may affect both physical and psychosocial functioning. Physical late effects include the development of subsequent malignancies as well as dysfunction of the cardiovascular, pulmonary, hepatic, renal, endocrine and reproductive systems[2]. Among these, reproductive health, and specifically pregnancy and delivery, represents a critical area for long-term follow-up care as having children is an important determinant of quality of life for CAYA cancer survivors[3-7].

Previous research indicates that CAYA cancer survivors can have difficulty conceiving or carrying a pregnancy to term as well as experiencing excess risk of adverse pregnancy outcomes. For example, the risks of premature birth and postpartum hemorrhage are both higher in CAYA cancer survivors compared to women who did not have cancer[8-13], and the risks increase 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 obstetric and perinatal complications, characterize the clinical features of those at risk, help survivors make informed decisions, facilitate counseling and timely referral to obstetric care specialized in high risk pregnancies, and facilitate opportunities for interventions to optimize pregnancy outcomes.

Unfortunately, few recommendations for obstetric care of CAYA cancer survivors exist. Obstetric risks in CAYA cancer survivors are generally noted in published clinical practice guidelines by North American and European groups[15-18], but without comprehensive assessment of the risk features of women who may benefit from high-risk obstetric follow-up. In a previous report, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) developed recommendations for cardiomyopathy surveillance[19], including early detection among women planning to become pregnant. In the current effect, the IGHG summarizes the results of a systematic review and presents a critical appraisal of available evidence on obstetric risks in CAYA cancer survivors (diagnosed before 25 years of age and not pregnant at that time), to synthesize these findings into evidence-based recommendations for surveillance and counseling of CAYA cancer survivors who are at risk for complications during pregnancy and delivery due to their cancer or cancer treatment.

METHODS

The aim of the IGHG is to establish a common vision and integrated strategy for the surveillance of late effects in childhood, adolescent and young adult cancer survivors. Methods

of the IGHG have been described previously[20]. This guideline focuses on the identification of 'at risk' CAYA cancer survivors diagnosed with cancer before age 25 years who would benefit from preconception counseling and high-risk surveillance during pregnancy. This guideline is focused on facilitating timely identification and referral of CAYA survivors at high-risk of obstetric complications. Management of obstetric complications is beyond the scope of the present guideline, which should defer to standards established by local/national health systems. Standardized definitions as used in this guideline are presented in Appendix 1, available upon request or online.

The obstetric guideline panel consisted of 33 experts from the United States of America, United Kingdom, Denmark, France, New Zealand, Australia, Japan and the Netherlands who represent relevant disciplines, including gynecology, obstetrics, midwifery, endocrinology, pediatric oncology, radiation oncology, epidemiology, and guideline methodology, as well as CAYA survivor/family representatives.

Concordances and discordances across existing survivorship guidelines of the North American Children's Oncology Group (COG)[15], the Dutch Childhood Oncology Group (DCOG)[16], the Scottish Intercollegiate Guidelines Network (SIGN)[18], and the UK Children's Cancer and Leukaemia Group (UKCCLG)[17] were evaluated. We defined the major outcomes for obstetric 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 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 (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. Studies published in English were selected for analysis. All abstracts were screened by two independent reviewers (ALLFK and one member of the working groups). Disagreements were resolved through consensus. Cross-reference checking was performed to identify additional studies that were potentially overlooked during the initial search. Each relevant article was summarized in one evidence table drafted by two reviewers (ALLFK and one member of the working groups), which also included a critical appraisal of risks of bias (Appendix 3). The evidence tables were subsequently assembled into summary of findings tables (ALLFK) and revised where necessary (RLM, LCMK). Next, we assessed the quality of the body of evidence for every clinical question according to criteria based on Grading of Recommendations Assessment Development and Evaluation (GRADE)[21] (Appendix 4).

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 to maintain flexibility across health care systems[22]. Terminology employed can be found in Appendix 5. Decisions were made through group discussion and final recommendations were discussed until unanimous consensus was reached. 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[20,22,23]. Pregnancy care-related recommendations from the IGHG cardiomyopathy guideline were adopted in this guideline in order to provide a complete overview of recommendations for pregnancy surveillance. The final harmonized recommendations were critically appraised by four independent external experts in the field and two survivor representatives.

FINDINGS

Discordances across existing LTFU guidelines

Identification of concordances and discordances amongst existing surveillance recommendations is displayed in Appendix 6, showing many discordant guideline areas for which we searched the evidence. The literature search yielded 2,772 abstracts for pregnancy and delivery related risks and 2,492 abstracts for congenital anomalies. In total, 98 full texts were reviewed and 28 articles were included (Figure 1, included articles in Appendix 7). The evidence tables and summary of findings are presented in Appendix 8. The conclusions of evidence tables including 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 obstetric surveillance?

Evidence for risks during pregnancy

Miscarriage

There is moderate level evidence that CAYA cancer survivors are at increased risk of miscarriage after radiotherapy to volumes exposing the uterus in comparison to the general population[9,14,24-30], although this association was only borderline statistically significant in a large cohort from the British Childhood Cancer Survivor Study[27] and not significant in two smaller studies[25,29]. There is only low level evidence for a dose-response relationship[30,31]. The evidence indicated no significant effect due to chemotherapy[9,27,31,32].

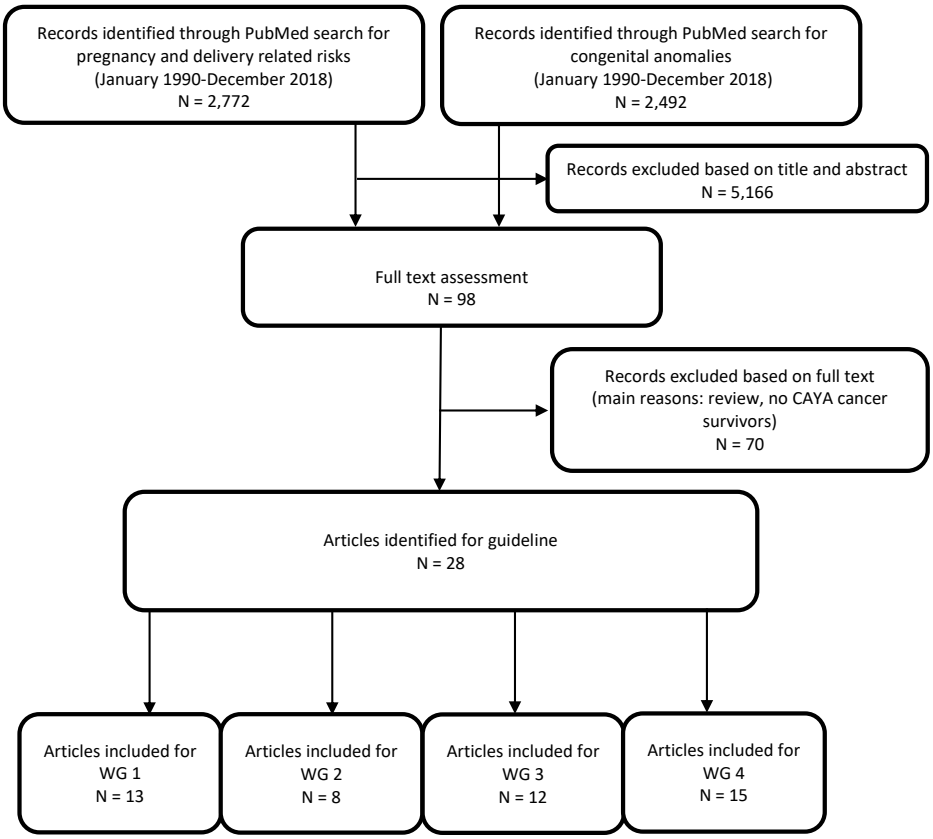

Figure 1. Flowchart of selected studies. Articles could be included for multiple working groups (WG). Four working groups respectively evaluated the following topics: 1) adverse fetal outcomes in pregnancy (such as miscarriage); 2) adverse maternal outcomes in pregnancy; 3) delivery outcomes; and 4)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

Termination of pregnancy

In the relevant articles, termination of pregnancy was defined as 'medically induced abortions' or 'not further defined', limiting, for instance, a distinction between medical and elective termination of pregnancy. In general, there is no suggestion for an increased risk of medically-induced terminations (very low level evidence)[14,24,27,30,33] in CAYA cancer survivors. However, there is (very) low level evidence for an increased risk of termination of pregnancy after any radiotherapy[14, 27] and chemotherapy[14,27].

Still birth

There is no suggestion for an increased risk of still birth (moderate level evidence) in CAYA cancer survivors in general[9,30], and low level evidence for increased risk of still birth after moderate to high doses ovarian-uterine radiotherapy (>10 Gy)[34] or abdominopelvic radiotherapy (>25 Gy)[31].

Table 1. Overall conclusions of evidence for obstetric 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 age 25 years	**Level of evidence***
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9, 25, 26, 28, 30, 33]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊖ MODERATE[9, 14, 24-30]
Increased risk with increasing *doses of abdominopelvic and pituitary radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[30, 31]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊕⊖ MODERATE[9, 14, 26, 27, 31]
Increased risk after *chemotherapy and radiotherapy* (no specific field) vs. no chemotherapy and radiotherapy.	⊕⊕⊖⊖ LOW[9, 14, 25, 26, 31]
No significant effect of *age at diagnosis*.	⊕⊕⊖⊖ LOW[9]
Risk of terminations in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊖⊖⊖ VERY LOW[30, 33]
Increased risk after *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[14, 27]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[14, 27]
Increased risk after chemotherapy and/or radiotherapy (to any field or gonadal) vs. no chemotherapy and radiotherapy.	⊕⊕⊖⊖ LOW[14, 24]
Risk of still birth in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9, 30]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 14, 27, 31, 42]
Increased risk after *high-dose ovarian-abdominal radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[31, 34, 42]
Increased risk after *abdominopelvic radiotherapy (>1.00 Gy)* given before menarche vs. no radiotherapy, but no significant effect when given after menarche	⊕⊕⊖⊖ LOW[34]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊖⊖ LOW[9, 14, 27, 31]
No significant effect of *alkylating agent dose*.	⊕⊕⊖⊖ LOW[34]
No significant effect of *alkylating agents in combination with abdominal-pelvic radiation* vs. no alkylating agents and abdominal-pelvic radiation.	⊕⊕⊖⊖ LOW[14, 24, 31]
Risk of gestational hypertension in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊖⊖⊖ VERY LOW[13, 36]
Increased risk after *abdominopelvic radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13, 35, 36]
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[36]
No significant effect of age at diagnosis.	⊕⊕⊖⊖ LOW[35]
Risk of pre-eclampsia in female cancer survivors diagnosed before age 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]

Table 1. Overall conclusions of evidence for obstetric risks in female childhood and adolescent cancer survivors (key outcomes) (continued)

Who needs preconception counseling? Who needs high-risk pregnancy surveillance?	
Risk of maternal anemia in female cancer survivors diagnosed before age 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, 35]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊕⊖⊖ LOW[11]
No significant effect of *radiotherapy and chemotherapy* vs. controls.	⊕⊕⊖⊖ LOW[11]
No significant effect of age at diagnosis.	⊕⊕⊕⊖ MODERATE[11, 35]
Risk of gestational diabetes in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[9, 11, 36]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 11, 35, 36]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊕⊕⊖ MODERATE[9, 11, 36]
Increased risk after chemotherapy in combination with radiotherapy vs. controls.	⊕⊖⊖⊖ VERY LOW[9, 11]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[9, 11, 35]
Risk of malposition in female cancer survivors diagnosed before age 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[35]
Increased risk with *increasing doses flank radiation*.	⊕⊖⊖⊖ VERY LOW[45]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[10, 35]
Risk of postpartum hemorrhage in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[8-10, 13, 35]
Increased risk after *abdominopelvic radiotherapy* vs. no radiotherapy.	⊕⊖⊖⊖ VERY LOW[13, 35]
No significant effect of age at diagnosis.	⊕⊕⊖⊖ LOW[35]
Risk of premature birth in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊕⊖ MODERATE[9-13, 28, 36]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[9, 11, 13, 29, 35, 36]
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, 36]
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 yrs at cancer diagnosis* vs. controls, but no significant effect in survivors aged <5 yrs at cancer diagnosis	⊕⊕⊖⊖ LOW[9, 11, 35]

Table 1. Overall conclusions of evidence for obstetric risks in female childhood and adolescent cancer survivors (key outcomes) (continued)

Who needs preconception counseling? Who needs high-risk pregnancy surveillance?	
Risk of low birth weight in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[9-13, 28, 36]
Increased risk after (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[9, 11, 13, 29, 31, 35, 36]
Increased risk after *increasing doses of abdominopelvic radiotherapy* (>2.5/25 Gy)	⊕⊕⊕⊖ MODERATE[12, 28, 31, 45]
Increased risk after *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[9, 11, 31, 36]
No significant effect alkylating agent dose.	⊕⊖⊖⊖ VERY LOW[12]
Increased risk after *radiotherapy and chemotherapy* vs. no radiotherapy and chemotherapy.	⊕⊖⊖⊖ VERY LOW[9, 11, 31]
Increased risk in *survivors aged ≥20 yrs at cancer diagnosis* vs. controls, but no significant effect in survivors aged <20 yrs at cancer diagnosis	⊕⊖⊖⊖ VERY LOW[9, 11, 35]
Risk of delivery of a child small for gestational age in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊖⊖ LOW[11, 12, 36]
No significant effect of (*abdominopelvic) radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[13, 29, 31, 36]
Increased risk after *increasing doses of abdominopelvic radiotherapy*.	⊕⊕⊖⊖ LOW[12, 31]
No significant effect of *chemotherapy* vs. no chemotherapy.	⊕⊖⊖⊖ VERY LOW[36]
No significant effect of alkylating agent dose.	⊕⊕⊖⊖ LOW[12]
No significant effect of radiotherapy and chemotherapy vs. surgery only.	⊕⊖⊖⊖ VERY LOW[31]
Risk of intrauterine growth restriction in female cancer survivors diagnosed before age 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 age 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 age 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 section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased likelihood of any cesarean section in in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[9-11, 36]
Increased likelihood after *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[9, 36]
Increased likelihood after *chemotherapy* vs. no chemotherapy,	⊕⊕⊖⊖ LOW[9, 36]
Significant effect of age at diagnosis (increased effect if 0-14 yrs at diagnosis)	⊕⊖⊖⊖ VERY LOW[9, 10]

Table 1. Overall conclusions of evidence for obstetric risks in female childhood and adolescent cancer survivors (key outcomes) (continued)

Who needs preconception counseling? Who needs high-risk pregnancy surveillance?	
Likelihood of an elective/primary cesarean section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
Increased likelihood in CAYA cancer survivors vs controls.	⊕⊕⊕⊕ HIGH[8, 10, 11, 35]
Increased likelihood after *radiotherapy* vs. no radiotherapy, specifically after abdominal radiotherapy in Wilms survivors.	⊕⊕⊕⊖ MODERATE[35]
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH[35]
Likelihood of an emergency/secondary/urgent cesarean section in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased likelihood in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE[8, 10, 13, 35]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[13, 35]
No significant effect of age at diagnosis.	⊕⊕⊕⊖ MODERATE[8, 35]
Risk of congenital anomalies/abnormalities in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊕ HIGH[9, 11, 13, 33, 37-41]
No significant effect of (*ovarian-abdominal) radiotherapy* vs. no radiotherapy.	⊕⊕⊕⊕ HIGH[13, 31, 37, 39, 40, 42, 43]
No significant effect of radiotherapy dose.	⊕⊕⊕⊖ MODERATE[31, 37, 42, 43, 45]
No significant effect of *alkylating agents* vs. no alkylating agents.	⊕⊕⊕⊖ MODERATE[31, 39, 40, 42, 43, 52]
No significant effect of alkylating agent dose.	⊕⊖⊖⊖ VERY LOW[43]
No significant effect of *alkylating agents in combination with abdominal-pelvic radiation* vs. no alkylating agents and abdominal-pelvic radiation.	⊕⊕⊕⊖ MODERATE[24, 31, 42]
No significant effect of age at diagnosis.	⊕⊖⊖⊖ VERY LOW[40]
Rate of supervision of high-risk pregnancy in female cancer survivors diagnosed before age 25 years	**Level of evidence**
No increased rates in CAYA cancer survivors vs controls.	⊕⊕⊖⊖ LOW[35]
No significant effect of *radiotherapy* vs. no radiotherapy.	⊕⊕⊖⊖ LOW[3]
Risk of retained placenta/manual removal of the placenta in female cancer survivors diagnosed before age 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 age 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 age 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 age 25 years	**Level of evidence**
Increased likelihood in CAYA cancer survivors vs. controls.	⊕⊖⊖⊖ VERY LOW[9]

*Citations refer to papers on which the GRADE level of evidence was based on, and do not necessarily support the overall conclusion.

Gestational hypertension

There is very low level evidence for an effect of radiotherapy on the risk of gestational hypertension in CAYA cancer survivors as compared to survivors treated without radiotherapy. The increased risk was only reported in the abdominopelvic irradiated survivors who had been diagnosed with Wilms tumor in the British Childhood Cancer Survivors Study[35], while two smaller studies did not find this association[13,36]. A report from the National Wilms Tumor Study Group observed an increased risk of any hypertensive disorder of pregnancy with increasing doses of flank radiotherapy, but as this was the only identified study assessing radiotherapy dose, the level of evidence is very low.

Pre-eclampsia

There is low level evidence for an increased risk of pre-eclampsia in CAYA cancer survivors as compared to controls, as this association was reported in one large population-based Australian study[9] but not in two other studies[11,13]. One of these studies included a small sub-cohort of 6 CAYA cancer survivors exposed to radiotherapy to the abdomen, none of whom developed pre-eclampsia[13]. No studies were identified that evaluated the risk of pre-eclampsia after alkylating agents.

Maternal anemia

There is low level evidence that abdominopelvic radiotherapy increases the risk of maternal anemia in CAYA cancer survivors as compared to non-irradiated survivors. This is based on increased risks observed in one large study[35] while the effect was not observed in another equally-sized cohort[11].

Gestational diabetes

There is low level evidence for an increased risk of gestational diabetes in CAYA cancer survivors as compared to controls, based on one report that found the association[9] and two that did not show a statistically significant association[11,36]. There is low level evidence for an effect of abdominopelvic radiotherapy[9,11,35,36]. There is moderate level evidence that there is no effect of chemotherapy on the risk of gestational diabetes[9,11,36] and high level evidence that there is no effect of age at diagnosis[9,11,35].

Malposition of the fetus

There is low and very low level evidence that there is no increased risk on malposition of the fetus, and that there is no effect of radiotherapy on this outcome[10,35].

Evidence for gestational length and birth weight

Premature birth

CAYA cancer survivors are at increased risk of premature birth (before 37 weeks of gestation) as compared to siblings and the general population (moderate level evidence)[9-13,28,29,36]. High level evidence showed that exposure to radiotherapy to volumes exposing the uterus increases the risk of premature birth[9,11,13,29,35,36]. Two reports did not include specific radiotherapy volumes, categorizing groups as treated with or without any type of radiotherapy; both also showed increased risk after treatment with radiotherapy[9,11]. We found low level evidence for a dose response relationship with radiotherapy, including one study that showed a trend for increasing risk with increasing flank radiation dose, specifically with doses >15 Gy[14]. Another study showed increased risks specifically with doses >5 Gy to the uterus and in a smaller sub-cohort before the onset of menarche a lower threshold of 2.5 Gy[12]. One study showed that chemotherapy (specific agents not further specified) was associated with an increased risk of premature birth (low level evidence)[11]. However, this effect was not found in a small Japanese study[36] and a large Australian population-based study[9]. One study investigated the effect of alkylating agent dose on the risk of premature birth and did not find a statistically significant effect (very low level evidence)[12].

Low birth weight

There is moderate level evidence for an increased risk of delivering a child with a low birth weight (below 2500 grams) in CAYA cancer survivors as compared to controls[9-13,28,36] and there is high level evidence for an effect of radiotherapy to volumes exposing the uterus[9,11,13,29,31,35,36]. A dose response relationship was observed in survivors of Wilms tumor[32] and a risk increasing effect of radiotherapy was specifically observed after >2.5 Gy[12] to the uterus and >25 Gy[31] abdominopelvic radiotherapy (moderate level evidence)[12,31]. While three studies did not identify chemotherapy as a risk factor for a low birth weight[9,31,36], the association was suggested in one report[11], yielding very low level evidence for this association. 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 birth weight[12].

Small for gestational age

There is low level evidence that there is no increased risk of delivering a child small for gestational age (SGA; <10th percentile birth weight for gestational age) among CAYA cancer survivors in general as compared to controls[11,12,36]. Although radiotherapy versus no radiotherapy was not found to be significantly associated with this outcome in four studies[13,29,31,36], two studies showed that patients treated with specific doses of abdominopelvic radiotherapy (>5 Gy and >25 Gy, respectively) had an increased risk of delivering a child small for gestational age (low level evidence)[12,31].

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 compared to controls[8,10]. Regarding assisted vaginal delivery rates, 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 sections (any cesarean section: from reports that did not make a distinction between elective (primary) and emergency (secondary/urgent) cesarean sections) among CAYA cancer survivors as compared to controls[9-11,36], especially after radiotherapy and chemotherapy (low level evidence)[9,36].

High level evidence was specifically identified for an increased rate of an elective cesarean delivery[8,10,11,35], especially after abdominopelvic radiotherapy (moderate level evidence)[35]. No statistically significant increased rate for the occurrence of emergency cesarean delivery (moderate level evidence) was found[8,10,13,35]. There was also no statistically significant effect of radiotherapy and age at diagnosis on rate of cesarean section (high level evidence)[8,13,35].

Evidence for risks related to delivery

Postpartum hemorrhage

There is low level evidence for an increased risk of postpartum hemorrhage in CAYA cancer survivors as compared to controls. An increased risk was observed in one report[8] but not in four others[9,10,13,35]. There is low level evidence for a statistically significant effect of abdominal radiotherapy, based on one small study suggesting an increased risk after this treatment[13], while one larger study did not find an increased risk[35].

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 as compared to controls. Nine studies, with large heterogeneity in outcome definitions, have reported on the prevalence of congenital anomalies and none showed an increased risk[9,11,13,33,37-41]. There is also high level evidence that there is no statistically significant effect of radiotherapy on the risk of congenital anomalies[13,31,37,39,40,42,43].

Evidence for additional obstetric outcomes

The evidence levels on the risk of retained placenta/manual removal of the placenta, placental pathologies, fetal growth restriction, uterine scar from previous surgery and

perineal laceration/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 only very limited number of papers are reported in Appendix 6 and also generated only low to very low levels of evidence.

Translating evidence into recommendations

The final recommendations are summarized in Table 2. Recommendations were formulated based on at least moderate levels of evidence for the risk of obstetric outcomes and its determinants (Table 1). 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 of gestation) and low birth weight (<2500 grams) after radiotherapy to volumes exposing the uterus. In addition, CAYA cancer survivors had higher rates of elective cesarean section (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 where a dose-response relationship was identified. Although low level evidence suggests a dose-response relationship of radiotherapy to volumes exposing the uterus[30,31], too little 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 all female CAYA cancer survivors have the right to be informed about their potential risk for adverse obstetric outcomes. Therefore, we recommend that healthcare providers should discuss the risk of adverse obstetric outcomes based on the specific cancer treatment exposures with all female CAYA cancer survivors of reproductive age (strong recommendation). Specifically regarding the risk of miscarriage, premature birth and low birth weight, the panel agreed that the benefits of preconception counseling and obstetric surveillance (i.e., early detection of fetal growth restriction or threatened premature delivery requiring intervention to ensure optimal neonatal outcome) clearly outweigh the potential harms (e.g., stress, anxiety and potential higher health care costs) for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus. The panel recommends that female CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus and their health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence). In addition, high risk obstetric surveillance is recommended for this patient group (strong recommendations).

Table 2. Harmonized recommendations for counseling and surveillance in pregnancy

General recommendation
Health care providers should discuss the risk of adverse obstetric 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 health care 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 health care providers should be aware of the risk of adverse obstetric outcomes including miscarriage (moderate quality evidence), premature birth (high quality evidence) and low birth weight (high quality evidence).
Who needs specific obstetric surveillance during pregnancy?
High risk obstetric surveillance is recommended for CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus due to the risk of premature birth and low birth weight (high quality evidence).
Who needs specific cardiac surveillance during pregnancy? *Based on IGHG cardiomyopathy guideline*[19]
Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation (moderate level recommendation, moderate quality evidence)[19].
No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal LV systolic function immediately prior to or during the first trimester of pregnancy (moderate level recommendation, low quality evidence)[19].

Panel: Gaps in knowledge and future directions for research of obstetric outcomes in CAYA cancer survivors

- Risks of medical and elective termination of pregnancy, including standardized definitions of this outcome and its confounders.
- Risks of gestational diabetes, gestational hypertension and pre-eclampsia, giving birth to babies small for gestational age, very premature delivery (<32 weeks of gestation) or postpartum hemorrhage.
- Effect of radiotherapy and dose-response relationships to specific volumes (e.g., uterus) on obstetric outcomes.
- Influence of relatively low doses of radiotherapy (including 10-15 Gy) that reach the uterus on obstetric outcomes.
- Effect of age at cancer diagnosis and pubertal stage at treatment on all obstetric risks.
- The contribution of environmental factors known to affect obstetric outcomes (e.g., BMI, smoking).
- The contribution of obstetric risk associated with artificial reproductive technology (ART), especially as fertility rates after ART (including donor oocytes) increase.
- Development of a risk prediction algorithm for outcomes including miscarriage, premature delivery and low birth weight, taking into account, e.g., age at cancer diagnosis, cancer treatment, maternal age, smoking, parity and ART.
- Methods to optimize timely provision of information about obstetric risk to CAYA cancer survivors in a variety of health care systems and health literacy settings.
- The effect of high risk surveillance on clinical relevant outcomes for survivors at risk.

Regarding the increased likelihood of elective cesarean section, the panel agreed that no recommendations could be drawn from this observation, as this may be attributable to many other factors such as the survivor's or the healthcare provider's concern.

Because the absence of an increased risk of congenital anomalies (high quality evidence) is of great importance to survivors, the panel agreed that female CAYA cancer survivors and their health care 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 (strong recommendation).

Based on previous recommendations from the IGHG for cardiomyopathy surveillance for CAYA cancer survivors, cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation (moderate recommendation)[19]. No recommendations have been formulated for the frequency of ongoing cardiomyopathy surveillance in pregnant survivors who have normal left ventricular systolic function immediately prior to or during the first trimester of pregnancy. However, the IGHG panel recommended that health care providers remain alert for cardiomyopathy in survivors treated with anthracyclines and/or chest-directed radiation who present with commonly reported symptoms such as shortness of breath, fatigue, and ankle swelling[19]. The panel additionally 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 post-partum, irrespective of lifetime anthracycline dose[19].

DISCUSSION

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, to optimize the quality of care and to minimize the burden of disease and unnecessary surveillance. The guideline panel, however, stressed the need for future research in larger cohorts to advance understanding about the radiotherapy dose response relationship to adverse obstetric 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[9,24,25,27,29,30,32]. The definition of a miscarriage was heterogeneous (if reported, mostly pregnancies ending before gestational week 20 but in the British Childhood Cancer Survivors Study (BCCSS) before 24 weeks), and the panel acknowledged the potential for reporting bias in both self-reported and registry-based data on this subject. However, increased risks were observed in three large cohorts, from the North American Childhood

Cancer Survivor Study (CCSS) (self-reported miscarriage, not further specified[14]), Australia (registered threatened miscarriage after 20 weeks of gestation[9]) and Denmark (registered spontaneous abortion, not further specified[30]). Although low level evidence suggests a dose-response relationship with radiotherapy to volumes exposing the uterus[30,31], 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.

Broad and overlapping definitions of termination of pregnancy and still birth, in addition to potential reporting bias for these sensitive topics, resulted in a low body of evidence on which to base recommendations, and these outcomes need further investigation (Panel). Still birth has been variably defined as the fetus not surviving after 20 weeks of gestation[9], after 28 weeks[30], or combined with neonatal deaths within the first 28 days of life in others[34]. Likewise the definition of termination of pregnancy has not been stated in some studies[14,30,33] or specifically defined as medically induced abortion in others[27]. Interestingly, a recent study in survivors aged 39 years or less at cancer diagnosis with robust outcome reporting showed a significantly reduced risk of termination of pregnancy[44], stressing the need for further research to more accurately define the prevalence of this outcome.

We identified high level evidence for the increased risks of premature birth and low birth weight after radiotherapy to volumes exposing the uterus[9-14,28,29,31,32,35,36]. The evidence for a dose-response relationship between radiotherapy and miscarriage, premature birth and low birth weight 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. For example, doses have been estimated using mathematical phantoms in cohorts from the CCSS and the National Wilms Tumor Study Group[12,45], approximated by determining the theoretic location of the relevant organ (e.g., uterus, ovary) on the dosimetry schemes[28] categorized in occasional very broad ranges such as 1-40 Gy for primary cancer treatment extending below the diaphragm[30] or abstracted from treatment records[31]. Consistent documentation of received organ volume dose distribution, as opposed to reconstructed organ dose, is important to assess more accurately the relationship of radiation dose and obstetric risk and is possible in modern clinical practice.

Radiotherapy to volumes exposing the ovaries is associated with premature ovarian insufficiency[46-49], but if fertility potential is retained, damage to the oocyte does not lead to increased risks of still birth or congenital anomalies as compared to the general population. Mechanisms leading to increased rates of miscarriage, premature delivery and low birth weight have not been completely elucidated, but several hypotheses have been proposed. Radiotherapy to volumes exposing the uterus can damage the uterine vasculature and muscular development[50], and potentially impair endometrial function due to impaired blood supply. This may result in poor implantation of the embryo and poor placental growth which could result in subsequent early miscarriage. The increased risks of premature birth

and low birth weight 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]. Additionally, hormonal deficiency as a consequence of ovarian failure may lead to smaller uterine volumes[51].

The panel has balanced the importance of preventing unnecessary consultations, visits and expenses for CAYA cancer survivors with the cost of failing to identify survivors at risk who would benefit from preconception consultation. As the clinical implication of awareness and preconception counseling can be tailored to the individual, the panel considered all CAYA cancer survivors treated with radiotherapy to volumes exposing the uterus to be at increased risk of miscarriage, premature delivery and low birth weight. In addition, CAYA cancer survivors treated with anthracyclines or chest-directed radiotherapy are at risk of perinatal cardiomyopathy. Cancer survivors should be counseled about obstetric 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 impact course of pregnancy. Communication among obstetric and oncology providers and survivors is key in these complicated cases.

Preconception consultation and obstetric surveillance may lead to referral to a specialized obstetric team rather than a midwifery team, and may 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 birth weight or cardiac monitoring, should adhere to established obstetric care guidelines.

No recommendations were formulated based on the high level of evidence concerning the increased likelihood of an elective cesarean section. Although many clinical, cultural and personal factors, which likely vary widely between health care systems, play a role in the decision for an elective cesarean section, health care providers may have been more cautious with this population knowing their increased obstetric risks. Reassuringly, no increased likelihood of an emergency cesarean section after radiotherapy was identified.

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[13,31,37,39,40,42,43]. As this is often a major concern in CAYA cancer survivors; therefore, 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 specifics regarding radiotherapy (dose and site) and chemotherapy (agents and dose), potential study biases without indication of response rates, and the scarcity of studies with multivariable analy-

ses 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. Another important topic is surveillance of thyroid dysfunction in CAYA cancer survivors, as latent hypothyroidism can impact fetal brain development[15,16]. Recommendations will be formulated in an upcoming IGHG guideline on surveillance of thyroid dysfunction. A periodic update of the obstetric 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). According to our findings, future studies should focus on the identification of threshold doses of radiotherapy to volumes exposing the uterus, the effect of different environmental factors such as lifestyle factors and the increasing use of assisted reproductive technology. 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

The presented IGHG effort was initiated to assist in the identification of specific adverse obstetric related outcomes that are increased in CAYA cancer survivors, and to identify the population that will benefit specifically from an individualized preconception consultation and pregnancy surveillance taking into account their treatment history.

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