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Counseling and surveillance of obstetric 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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Counseling and surveillance of obstetric 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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 2 **adolescent, and young adult cancer survivors: recommendations from the**
 3 **International Late Effects of Childhood Cancer Guideline Harmonization**

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84

85

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90 **Condensation:** Female cancer survivors have increased risks of premature delivery and low
91 birth weight associated with radiotherapy exposing the uterus, which warrant high-risk
92 pregnancy surveillance.

93 **Running head:** IGHG recommendations for management of obstetric risks for female CAYA
94 survivors

95

96 **AJOG at a glance:**

97 **Why was this study conducted?** National guidelines that identify specific adverse pregnancy
98 outcomes and the clinical characteristics of childhood, adolescent, and young adult (CAYA)
99 cancer survivors are scarce and vary in content.

100 **What are the key findings?** There are increased risks of premature delivery and low birth
101 weight associated with radiotherapy exposing the uterus and pregnancy-related
102 cardiomyopathy following treatment with anthracyclines.

103 **What does this study add to what is already known?** This guideline from the International
104 Late Effects of Childhood Cancer Guideline Harmonization Group identifies specific adverse
105 obstetric related outcomes that are increased in CAYA cancer survivors, to characterize the
106 population that will benefit specifically from an individualized preconception consultation
107 and pregnancy surveillance.

108 **Keywords:** prenatal care; late effects; childhood cancer survivors; fecundity; pregnancy;

109 **ABSTRACT**

110 **Objective:** Female childhood, adolescent, and young adult (CAYA) cancer survivors have an
111 increased risk of adverse pregnancy outcomes related to their cancer or treatment-
112 associated sequelae. Optimal care for CAYA cancer survivors can be facilitated by clinical
113 practice guidelines that identify specific adverse pregnancy outcomes and the clinical
114 characteristics of at-risk subgroups. However, national guidelines are scarce and vary in
115 content. Here, the International Late Effects of Childhood Cancer Guideline Harmonization
116 Group (IGHG) offers recommendations for the counselling and surveillance of obstetric risks
117 of CAYA survivors.

118 **Data sources:** A systematic literature search in MEDLINE (through PubMed) to identify all
119 available evidence published between January 1990 and December 2018.

120 **Study eligibility criteria:** Published articles on pregnancy, perinatal or congenital risks in
121 female cancer survivors were screened for eligibility. Study designs with a sample size larger
122 than 40 pregnancies in CAYA cancer survivors (diagnosed before age 25, not pregnant at that
123 time) were eligible.

124 **Study appraisal and synthesis methods:** This guideline from the IGHG systematically
125 appraised the quality of available evidence for adverse obstetric outcomes in CAYA cancer
126 survivors using GRADE methodology, and formulated recommendations to enhance
127 evidence-based obstetric care and preconception counseling of female CAYA cancer
128 survivors.

129 **Results:** Healthcare providers should discuss the risk of adverse obstetric outcomes based on
130 cancer treatment exposures with all female CAYA cancer survivors of reproductive age,
131 before conception. Health care providers should be aware that there is no evidence to
132 support an increased risk of giving birth to a child with congenital anomalies (high quality

133 evidence). Survivors treated with radiotherapy to volumes exposing the uterus and their
134 health care providers should be aware of the risk of adverse obstetric outcomes including
135 miscarriage (moderate quality evidence), premature birth (high quality evidence) and low
136 birth weight (high quality evidence); therefore, high risk obstetric surveillance is
137 recommended. Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first
138 trimester for all female survivors treated with anthracyclines and/or chest radiation.

139 **Conclusions:** Female cancer survivors have increased risks of premature delivery and low
140 birth weight associated with radiotherapy targeting the lower body and thereby exposing
141 the uterus, which warrant high-risk pregnancy surveillance.

142

143 INTRODUCTION

144 Five year survival rates for childhood, adolescent, and young adult (CAYA) cancer patients
145 now approach 80%¹. Consequently, increasing numbers of CAYA cancer survivors are at risk
146 for adverse physical and psychosocial complications from their cancer and/or its treatment².
147 Reproductive health, and specifically pregnancy and delivery outcomes, represent a critical
148 area for long-term follow-up as having children is an important determinant of quality of life
149 for CAYA cancer survivors³⁻⁷.

150 Previous research indicates difficulty conceiving or carrying a pregnancy to term, as well as
151 excess risk of adverse pregnancy outcomes, among CAYA cancer survivors . For example, the
152 risks of premature birth and postpartum hemorrhage are higher in CAYA cancer survivors
153 compared to women who did not have cancer⁸⁻¹³, and these risks are further increased in
154 survivors treated with abdominopelvic radiotherapy^{9, 11-14}. Evidence-based clinical guidelines
155 on surveillance in pregnancy can identify the type and prevalence of specific obstetric and
156 perinatal complications, characterize the clinical features of those at risk, help survivors
157 make informed decisions, facilitate counseling and timely referral to high-risk obstetric care,
158 and enable opportunities for interventions to optimize pregnancy outcomes.

159

160 OBJECTIVE

161 Published clinical practice guidelines by North American and European cancer groups
162 reference general obstetric risks¹⁵⁻¹⁸, but do not comprehensively assess the clinical features
163 of those who could benefit from high-risk obstetric follow-up. Herein, we summarize the
164 results of a systematic review undertaken by the International Late Effects of Childhood
165 Cancer Guideline Harmonization Group (IGHG) and present a critical appraisal of available
166 evidence on obstetric risks in CAYA cancer survivors, synthesizing these findings into

167 evidence-based recommendations for surveillance and counseling of CAYA cancer survivors
168 during pregnancy and delivery due to their cancer or cancer treatment.

169

170 **METHODS**

171 This guideline focuses on facilitating timely identification of CAYA cancer survivors at high-
172 risk of obstetric complications diagnosed with cancer before age 25 years (and not pregnant
173 at that time) who would benefit from preconception counseling and surveillance during
174 pregnancy. Management of obstetric complications is beyond the scope of the present
175 guideline, which should defer to standards established by local/national health systems.
176 Standardized definitions used in this guideline are presented in **Appendix 1**.

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

182 Methods of the IGHG have been described previously¹⁹. For this guideline, concordances and
183 discordances across existing survivorship guidelines of the North American Children's
184 Oncology Group (COG)¹⁵, the Dutch Childhood Oncology Group (DCOG)¹⁶, the Scottish
185 Intercollegiate Guidelines Network (SIGN)¹⁸, and the UK Children's Cancer and Leukaemia
186 Group (UKCCLG)¹⁷ were evaluated. We defined the major outcomes for obstetric problems
187 in survivors and congenital problems in offspring (**Appendix 1**). For all discordances and
188 relevant outcomes, focused clinical questions were formulated to determine whether
189 specific preconception consultation or surveillance was indicated. Four working groups
190 evaluated the following topics: 1) adverse fetal outcomes in pregnancy (such as miscarriage);

191 2) adverse maternal outcomes in pregnancy; 3) delivery outcomes; and 4) congenital
192 anomalies of the neonate.

193 A systematic literature search was performed in MEDLINE (through PubMed) to identify all
194 available evidence published between January 1990 and December 2018, using the search
195 terms “childhood cancer”, “survivors”, “late effects” and “obstetric problems”. Details of the
196 full search strategy are included in **Appendix 2**. All study designs with a sample size larger
197 than 40 pregnancies in female childhood cancer survivors were eligible. To ensure rigorous
198 review of manuscripts by at least two individuals, only studies published in English were
199 selected for analysis. All abstracts were screened by two independent reviewers (ALLFK and
200 one working group member). Disagreements were resolved through consensus. Cross-
201 reference checking was performed to identify additional studies overlooked during the initial
202 search. Relevant articles were summarized in one evidence table by two reviewers (ALLFK
203 and one working group member), including a critical appraisal of risks of bias (**Appendix 3**).
204 The evidence tables were subsequently assembled into summary of findings tables (ALFFK)
205 and revised where necessary (RLM, LCMK). We assessed the quality of the body of evidence
206 for each clinical question according to criteria based on Grading of Recommendations
207 Assessment Development and Evaluation (GRADE)²⁰ (**Appendix 4**). The quality of the total
208 body of evidence is graded according to four levels: High (⊕⊕⊕⊕), further research is
209 unlikely to change the confidence in the estimate of effect; Moderate (⊕⊕⊕⊖), further
210 research is likely to have an important impact on the confidence in the estimate of effect
211 and may change the estimate; Low (⊕⊕⊖⊖), further research is very likely to have an
212 important impact on the confidence in the estimate of effect and is likely to change the
213 estimate; and Very low (⊕⊖⊖⊖), any estimate of effect is very uncertain. The level of
214 evidence decreased in the presence of study limitations (risk of bias in the studies),

215 inconsistency of results between studies, indirectness of the study populations or outcomes,
216 or imprecision of the effect estimates. The level of evidence increased if the effect sizes
217 were large or there was evidence for a dose-response relationship.

218

219 *Translating evidence into recommendations*

220 Recommendations were drafted considering the level of the evidence, other effects of the
221 expected risks (such as unnecessary medicalization), and the need for flexibility across
222 health care systems²¹. Terminology employed for radiotherapy and obstetric outcomes can
223 be found in **Appendix 5**. Decisions were made through iterative group discussions, final
224 recommendations represent unanimous consensus. The strength of the recommendations
225 was graded according to published evidence-based methods (**Appendix 4**).
226 Recommendations were classified into strong or moderate recommendations, and based on
227 high quality evidence, moderate quality evidence or expert opinion^{19, 21, 22}. Pregnancy care-
228 related recommendations from the IGHG cardiomyopathy guideline were adopted in this
229 guideline to provide a complete overview of recommendations for pregnancy surveillance.
230 The final harmonized recommendations were critically appraised by four independent
231 external experts in the field and two survivor representatives.

232

233 **RESULTS**

234 *Discordances across existing LTFU guidelines*

235 Identification of concordances and discordances amongst existing surveillance
236 recommendations is displayed in **Appendix 6**. The literature search yielded 2,772 abstracts
237 for pregnancy and delivery related risks and 2,492 abstracts for congenital anomalies. In
238 total, 98 full texts were reviewed, and 28 articles were included (**Figure 1, included articles**

239 **in Appendix 7)**. The evidence tables and summary of findings are presented in **Appendix 8**.
240 The conclusions of evidence tables including GRADE assessment are summarized in **Table 1**
241 and **Appendix 9** and depicted in a color scheme in **Appendix 10**.

242

243 **Who needs preconception consultation or specific obstetric surveillance?**

244 **Evidence for risks during pregnancy**

245 *Miscarriage*

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

252

253 *Termination of pregnancy*

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

260

261 *Stillbirth*

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

266

267 *Gestational hypertension*

268 There is very low level evidence for an effect of radiotherapy on the risk of gestational
269 hypertension in CAYA cancer survivors as compared to survivors treated without
270 radiotherapy. The increased risk was only reported in the abdominopelvic irradiated
271 survivors who had been diagnosed with Wilms tumor in the BCCSS³⁴, while two smaller
272 studies did not find this association^{13, 35}. A paper from the National Wilms Tumor Study
273 Group observed an increased risk of any hypertensive disorder of pregnancy with increasing
274 doses of flank radiotherapy, but as this was the only identified study assessing radiotherapy
275 dose, the level of evidence is very low.

276

277 *Pre-eclampsia*

278 There is low level evidence for an increased risk of pre-eclampsia in CAYA cancer survivors as
279 compared to controls, as this association was reported in one large population-based
280 Australian study⁹ but not in two other studies^{11, 13}. Of note, one of these studies concerned a
281 small sub-cohort of 6 CAYA cancer survivors exposed to radiotherapy to the abdomen, none
282 of whom developed pre-eclampsia¹³. No studies were identified that evaluated the risk of
283 pre-eclampsia after chemotherapy.

284

285 *Maternal anemia*

286 There is low level evidence that abdominopelvic radiotherapy increases the risk of maternal
287 anemia in CAYA cancer survivors as compared to non-irradiated survivors. This is based on
288 increased risks observed in one large study³⁴ while the effect was not observed in another
289 equally-sized cohort¹¹.

290

291 *Gestational diabetes*

292 There is low level evidence overall for an increased risk of gestational diabetes in CAYA
293 cancer survivors as compared to controls, based on one report that found the association⁹
294 and two that did not show an association^{11, 35}. There is low level evidence for an effect of
295 abdominopelvic radiotherapy^{9, 11, 34, 35}, moderate level evidence that there is no effect of
296 chemotherapy,^{9, 11, 35} and high level evidence that there is no effect of age at diagnosis^{9, 11, 34}
297 on the risk of gestational diabetes.

298

299 *Malposition of the fetus*

300 There is no increased risk of malposition of the fetus (low level evidence), and no effect of
301 radiotherapy on this outcome (very low level evidence)^{10, 34}.

302

303 **Evidence for gestational length and birth weight**

304 *Premature birth*

305 CAYA cancer survivors are at increased risk of premature birth (before 37 weeks of
306 gestation) as compared to siblings and the general population (moderate level evidence)^{9-13,}
307 ^{27, 28, 35}. High level evidence showed that radiotherapy to volumes exposing the uterus
308 increases the risk of premature birth^{9, 11, 13, 28, 34, 35}. Two reports did not delineate specific
309 radiotherapy volumes, categorizing groups only as treated with or without any type of

310 radiotherapy; but both also showed increased risk after treatment with radiotherapy^{9,11}. We
311 found low level evidence for a dose response relationship with radiotherapy, including one
312 study that showed a trend for increasing risk with increasing flank radiation dose, specifically
313 with doses >15 Gy¹⁴. Another study showed increased risks specifically with doses >5 Gy to
314 the uterus and in a smaller sub-cohort treated prior to menarche, an even lower threshold
315 of 2.5 Gy¹². One study showed that chemotherapy was associated with an increased risk of
316 premature birth (low level evidence)¹¹. However, this effect was not found in a small
317 Japanese study³⁵ or in a large Australian population-based study⁹. One study did not observe
318 a significant effect of alkylating agent dose on risk of premature birth (very low level
319 evidence)¹².

320

321 *Low birth weight*

322 There is moderate level evidence for an increased risk of low birth weight (below 2500
323 grams) delivery in CAYA cancer survivors as compared to controls^{9-13, 27, 35} and high level
324 evidence for this outcome after radiotherapy to volumes exposing the uterus^{9, 11, 13, 28, 30, 34,}
325 ³⁵. A dose response relationship was observed in survivors of Wilms tumor³¹ and risk of an
326 effect of radiotherapy was observed after >2.5 Gy¹² to the uterus and >25 Gy³⁰
327 abdominopelvic radiotherapy (moderate level evidence)^{12, 30}. While three studies did not
328 identify chemotherapy as a risk factor for low birth weight^{9, 30, 35}, the association was
329 suggested in one report¹¹(very low level evidence). There also seems to be no effect of
330 alkylating agent dose (very low level evidence) on the risk of giving birth to a child with a low
331 birth weight¹².

332

333 *Small for gestational age*

334 There is low level evidence for no increased risk of small for gestational age (SGA; <10th
335 percentile birth weight for gestational age) delivery among CAYA cancer survivors in general
336 as compared to controls^{11, 12, 35}. Although radiotherapy versus no radiotherapy was not
337 found to be significantly associated with this outcome in four studies^{13, 28, 30, 35}, two studies
338 showed that patients treated with specific doses of abdominopelvic radiotherapy (>5 Gy and
339 >25 Gy, respectively) did have an increased risk (low level evidence)^{12, 30}.

340

341 **Evidence for mode of delivery**

342 *Vaginal delivery*

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

347

348 *Cesarean delivery*

349 There is low level evidence for higher rates of “any cesarean section” (data from reports that
350 did not distinguish between elective (primary) and emergency (secondary/urgent) cesarean
351 sections) among CAYA cancer survivors as compared to controls^{9-11, 35}, including reports
352 evaluating prevalence after radiotherapy and chemotherapy (low level evidence)^{9, 35}.

353 High level evidence was identified for an increased rate of an elective cesarean delivery^{8, 10,}
354 ^{11, 34}, especially after abdominopelvic radiotherapy (moderate level evidence)³⁴. No
355 significantly increased rate was observed for the occurrence of emergency cesarean delivery
356 (moderate level evidence)^{8, 10, 13, 34}. Radiotherapy nor age at diagnosis significantly affected
357 the rate of emergency cesarean section (high level evidence)^{8, 13, 34}

358

359 Evidence for risks related to delivery*360 Postpartum hemorrhage*

361 There is low level evidence for an increased risk of postpartum hemorrhage in CAYA cancer
362 survivors as compared to controls. An increased risk was observed in one report⁸ but not in
363 four others^{9, 10, 13, 34}. There is low level evidence for a statistically significant effect of
364 abdominal radiotherapy for this outcome based on one small study suggesting an increased
365 risk¹³, while another larger study did not find an increased risk³⁴.

366

367 Evidence for problems of the neonate*368 Congenital anomalies*

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

375

376 Evidence for additional obstetric outcomes

377 The evidence levels on the risk of retained placenta/manual removal of the placenta,
378 placental pathologies, fetal growth restriction, uterine scar from previous surgery and
379 perineal laceration/rupture were low to very low or revealed no increased risk for these
380 outcomes. Concerning the neonate, the evidence levels on the risk of resuscitation and
381 admission to a special care unit were very low. Additional outcomes evaluated in a very

382 limited number of papers are reported in **Appendix 6**, also demonstrating only low to very
383 low levels of evidence.

384

385 **Translating evidence into recommendations**

386 Final recommendations, formulated based on at least moderate or high levels of evidence
387 for the risk of obstetric outcomes and its determinants (**Table 1**) are summarized in **Table 2**.

388 There was moderate level evidence for an increased risk of miscarriage after radiotherapy to
389 volumes exposing the uterus, and high level evidence for an increased risk of premature
390 birth (<37 weeks of gestation) and low birth weight (<2500 grams) after radiotherapy to
391 volumes exposing the uterus. In addition, CAYA cancer survivors had higher rates of elective
392 cesarean section (high level evidence). There was high level evidence that there is no
393 increased risk of congenital anomalies in the offspring of CAYA cancer survivors. Lower levels
394 of evidence were included for the identification of gaps in knowledge and future research
395 directions (**Panel**). Radiotherapy was of specific interest if and when a dose-response
396 relationship was identified. Although low level evidence suggests a dose-response
397 relationship of radiotherapy to volumes exposing the uterus with the risk of miscarriage²⁹,
398 ³⁰, insufficient evidence is available to identify a safe threshold dose.

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

405 For example, female CAYA cancer survivors treated with radiotherapy to volumes exposing
406 the uterus and their health care providers should be aware of the risk of adverse obstetric
407 outcomes including miscarriage (moderate quality evidence), premature birth (high quality
408 evidence) and low birth weight (high quality evidence). In addition, high risk obstetric
409 surveillance is recommended for this patient group (strong recommendations). The panel
410 agreed that the benefits of preconception counseling and obstetric surveillance for these
411 outcomes (i.e., early detection of fetal growth restriction or threatened premature delivery
412 requiring intervention to ensure optimal neonatal outcome) clearly outweigh the potential
413 harms (e.g., stress, anxiety and potential higher health care costs).

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

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

420 Based on previous recommendations from the IGHG for cardiomyopathy surveillance for
421 CAYA cancer survivors, cardiomyopathy surveillance is reasonable prior to pregnancy or in
422 the first trimester for all female survivors treated with anthracyclines and/or chest radiation
423 (moderate recommendation)⁴³. No recommendations have been formulated for the
424 frequency of ongoing cardiomyopathy surveillance in pregnant survivors who have normal
425 left ventricular systolic function immediately prior to or during the first trimester of
426 pregnancy. However, the IGHG panel recommended that health care providers remain alert
427 for cardiomyopathy in survivors treated with anthracyclines and/or chest-directed radiation
428 who present with commonly reported symptoms such as shortness of breath, fatigue, and

429 ankle swelling⁴³. The panel additionally emphasized that CAYA cancer survivors with
430 compromised left ventricular systolic function (<30%) before pregnancy are more likely to
431 have further reduction in cardiac function during pregnancy or post-partum, irrespective of
432 lifetime anthracycline dose⁴³.

433

434 **COMMENT**

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

442 Critical evaluation of the published literature aided by the GRADE methodology yielded
443 moderate level evidence that CAYA cancer survivors are at increased risk of miscarriage after
444 radiotherapy^{9, 23, 24, 26, 28, 29, 31}. When reported, the definition of a miscarriage was
445 heterogeneous (usually pregnancies ending before gestational week 20 or, in the BCCSS,
446 before 24 weeks) and the panel acknowledged the potential for reporting bias in both self-
447 reported and registry-based data. However, increased risks were observed in three large
448 cohorts, from the North American Childhood Cancer Survivor Study (CCSS) (self-reported
449 miscarriage, not further specified¹⁴), Australia (registered threatened miscarriage after 20
450 weeks of gestation⁹) and Denmark (registered spontaneous abortion, not further
451 specified²⁹). Although low level evidence suggests a dose-response relationship with
452 radiotherapy to volumes exposing the uterus^{29, 30}, there is insufficient evidence to identify a

453 safe threshold dose. Even though there is no specific action to reduce this risk, the panel
454 agreed survivors need to be counseled of their potential increased risk of miscarriage.

455 Lack of definition of termination of pregnancy^{14, 29, 32} and broad and overlapping definitions
456 of stillbirth (e.g. the fetus not surviving after 20 weeks of gestation⁹, after 28 weeks²⁹, or
457 combined with neonatal deaths within the first 28 days of life³³), and potential reporting bias
458 resulted in a low body of evidence on which to base recommendations (**Panel**).

459 Interestingly, a recent study in survivors aged 39 years or less at cancer diagnosis with robust
460 outcome reporting showed a significantly reduced risk of termination of pregnancy⁴⁴,
461 stressing the need for further research to define more accurately the prevalence of this
462 outcome.

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

472 Radiotherapy to volumes exposing the ovaries, that is, radiotherapy targeting the lower
473 body and thereby exposing the ovaries to substantial amounts of ionizing radiation, is
474 associated with premature ovarian insufficiency⁴⁶⁻⁴⁹ but does not lead to increased risks of
475 stillbirth or congenital anomalies as compared to the general population. Mechanisms
476 leading to increased rates of miscarriage, premature delivery and low birth weight have not

477 been completely elucidated, but several hypotheses have been proposed. Radiotherapy to
478 volumes exposing the uterus can damage the uterine vasculature and muscular
479 development⁵⁰, and potentially impair endometrial function due to impaired blood supply.
480 This may result in poor implantation of the embryo and poor placental growth which could
481 contribute to subsequent early miscarriage. The increased risks of premature birth and low
482 birth weight may result from uterine vasculature injury leading to impaired utero-placental
483 blood flow, insufficient placental development and hence fetal growth restriction, or may
484 result from a reduced uterine elasticity and volume^{50, 51}. Additionally, hormonal deficiency as
485 a consequence of ovarian failure may lead to smaller uterine volumes⁵¹.

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

496 No recommendations were formulated based on the high level of evidence concerning the
497 increased likelihood of an elective cesarean section. The increased obstetric risks of cancer
498 survivors may influence the varied clinical, cultural and personal factors for patients and
499 providers that contribute to decision making about elective cesarean sections. Reassuringly,

500 the likelihood of an emergency cesarean section was not increased among women treated
501 with radiotherapy.

502 A large and consistent body of evidence indicates that neonates of CAYA cancer survivors
503 treated with and without radiotherapy are not at increased risk of congenital anomalies^{13, 30,}
504 ^{36, 38, 39, 41, 42}. As this is often a major concern in CAYA cancer survivors, the panel
505 recommends reassurance of CAYA cancer survivors that there is no indication of such an
506 increased risk.

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

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

527

528 **CONCLUSION**

529 This IGHG analysis identified specific adverse obstetric related outcomes that are increased
530 in CAYA cancer survivors to characterize the population that will benefit specifically from an
531 individualized preconception consultation and pregnancy surveillance. Key findings are that
532 there are increased risks of premature delivery and low birth weight associated with
533 radiotherapy targeting the lower body and thereby exposing the uterus, which warrant high-
534 risk pregnancy surveillance, and that survivors should be reassured there is no increased risk
535 of congenital abnormality.

536

537

538 *Contributors*

539 ALLFK, RLM, LCMK, MMH, MMHE, and JL contributed to the conception and design of the
540 study. All authors contributed to the search strategy, data extractions, interpretations of the
541 data, formulation of the recommendations and critically revised the report. All authors
542 approved the final version.

543

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548

549 *Declaration of interests*

550 The authors have no competing interests to declare.

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685

686

687 **Table 1.** Overall conclusions of evidence for obstetric risks in female childhood and adolescent cancer
 688 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, 24, 25, 27, 29, 32}
Increased risk after (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ MODERATE ^{9, 14, 23-29}
Increased risk with increasing doses of <i>abdominopelvic</i> and <i>pituitary</i> radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{29, 30}
No significant effect of <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊖ MODERATE ^{9, 14, 25, 26, 30}
Increased risk after <i>chemotherapy</i> and <i>radiotherapy</i> (no specific field) vs. no chemotherapy and radiotherapy.	⊕⊕⊕⊖ LOW ^{9, 14, 24, 25, 30}
No significant effect of <i>age at diagnosis</i> .	⊕⊕⊕⊖ 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 ^{29, 32}
Increased risk after <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{14, 26}
Increased risk after <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊖ VERY LOW ^{14, 26}
Increased risk after chemotherapy and/or radiotherapy (to any field or gonadal) vs. no chemotherapy and radiotherapy.	⊕⊕⊕⊖ LOW ^{14, 23}
Risk of stillbirth in female cancer survivors diagnosed before age 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs controls.	⊕⊕⊕⊖ MODERATE ^{9, 29}
No significant effect of <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{9, 14, 26, 30, 41}
Increased risk after <i>high-dose ovarian-abdominal</i> radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{30, 33, 41}
Increased risk after <i>abdominopelvic</i> radiotherapy (>1.00 Gy) given before menarche vs. no radiotherapy, but no significant effect when given after menarche	⊕⊕⊕⊖ LOW ³³
No significant effect of <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊖ LOW ^{9, 14, 26, 30}
No significant effect of <i>alkylating agent</i> dose.	⊕⊕⊕⊖ LOW ³³
No significant effect of <i>alkylating agents in combination with abdominal-pelvic radiation</i> vs. no alkylating agents and abdominal-pelvic radiation.	⊕⊕⊕⊖ LOW ^{14, 23, 30}
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, 35}
Increased risk after <i>abdominopelvic</i> radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ VERY LOW ^{13, 34, 35}
Increased risk with <i>increasing doses of flank</i> radiotherapy in CAYA Wilms tumor survivors.	⊕⊕⊕⊖ VERY LOW ⁴⁵
No significant effect of <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊖ VERY LOW ³⁵
No significant effect of <i>age at diagnosis</i> .	⊕⊕⊕⊖ LOW ³⁴
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 <i>abdominopelvic</i> radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ VERY LOW ¹³
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 (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{11, 34}
Increased risk after <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊖ LOW ¹¹
No significant effect of <i>radiotherapy and chemotherapy</i> vs. controls.	⊕⊕⊕⊖ LOW ¹¹
No significant effect of <i>age at diagnosis</i> .	⊕⊕⊕⊖ MODERATE ^{11, 34}
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, 35}
Increased risk after (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊖ LOW ^{9, 11, 34, 35}

No significant effect of <i>chemotherapy</i> 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 age 25 years	Level of evidence
No increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊕⊕ VERY LOW ¹⁰
No significant effect of <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊕ LOW ³⁴
Increased risk with <i>increasing doses flank radiation</i> .	⊕⊕⊕⊕ VERY LOW ⁴⁵
No significant effect of age at diagnosis.	⊕⊕⊕⊕ HIGH ^{10, 34}
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, 34}
Increased risk after <i>abdominopelvic radiotherapy</i> 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 age 25 years	Level of evidence
Increased risk in CAYA cancer survivors vs. controls.	⊕⊕⊕⊕ MODERATE ^{9-13, 27, 35}
Increased risk after (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊕ HIGH ^{9, 11, 13, 28, 34, 35}
Increased risk with <i>increasing doses of ovarian-abdominal radiotherapy (>5/15 Gy)</i> .	⊕⊕⊕⊕ LOW ^{12, 45}
Increased risk after <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊕ LOW ^{9, 11, 35}
No significant effect of <i>alkylating agent dose</i> .	⊕⊕⊕⊕ LOW ¹²
Increased risk after <i>radiotherapy and chemotherapy</i> vs. no radiotherapy and chemotherapy.	⊕⊕⊕⊕ MODERATE ^{9, 11}
Increased risk in <i>survivors aged >5 yrs at cancer diagnosis</i> vs. controls, but no significant effect in survivors aged <5 yrs at cancer diagnosis	⊕⊕⊕⊕ LOW ^{9, 11, 34}
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, 27, 35}
Increased risk after (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊕ HIGH ^{9, 11, 13, 28, 30, 34, 35}
Increased risk after <i>increasing doses of abdominopelvic radiotherapy (>2.5/25 Gy)</i>	⊕⊕⊕⊕ MODERATE ^{12, 27, 30, 45}
Increased risk after <i>chemotherapy</i> vs. no chemotherapy.	⊕⊕⊕⊕ VERY LOW ^{9, 11, 30, 35}
No significant effect alkylating agent dose.	⊕⊕⊕⊕ VERY LOW ¹²
Increased risk after <i>radiotherapy and chemotherapy</i> vs. no radiotherapy and chemotherapy.	⊕⊕⊕⊕ VERY LOW ^{9, 11, 30}
Increased risk in <i>survivors aged ≥20 yrs at cancer diagnosis</i> vs. controls, but no significant effect in survivors aged <20 yrs at cancer diagnosis	⊕⊕⊕⊕ VERY LOW ^{9, 11, 34}
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, 35}
No significant effect of (<i>abdominopelvic</i>) radiotherapy vs. no radiotherapy.	⊕⊕⊕⊕ LOW ^{13, 28, 30, 35}
Increased risk after <i>increasing doses of abdominopelvic radiotherapy</i> .	⊕⊕⊕⊕ LOW ^{12, 30}
No significant effect of <i>chemotherapy</i> 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 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	Level of evidence

age 25 years	
No increased likelihood of in CAYA cancer survivors vs. controls.	⊕⊕⊕⊕ MODERATE ^{8, 10, 13}
No significant effect of <i>radiotherapy</i> 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, 35}
Increased likelihood after <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊕ LOW ^{9, 35}
Increased likelihood after <i>chemotherapy</i> vs. no chemotherapy,	⊕⊕⊕⊕ LOW ^{9, 35}
Significant effect of age at diagnosis (increased effect if 0-14 yrs at diagnosis)	⊕⊕⊕⊕ VERY LOW ^{9, 10}
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, 34}
Increased likelihood after <i>radiotherapy</i> 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 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, 34}
No significant effect of <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊕ HIGH ^{13, 34}
No significant effect of age at diagnosis.	⊕⊕⊕⊕ MODERATE ^{8, 34}
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, 32, 36-40}
No significant effect of (<i>ovarian-abdominal</i>) <i>radiotherapy</i> 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 <i>alkylating agents</i> vs. no alkylating agents.	⊕⊕⊕⊕ MODERATE ^{30, 38, 39, 41, 42, 52}
No significant effect of alkylating agent dose.	⊕⊕⊕⊕ VERY LOW ⁴²
No significant effect of <i>alkylating agents in combination with abdominal-pelvic radiation</i> 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 age 25 years	Level of evidence
No increased rates in CAYA cancer survivors vs controls.	⊕⊕⊕⊕ LOW ³⁴
No significant effect of <i>radiotherapy</i> vs. no radiotherapy.	⊕⊕⊕⊕ LOW ³⁴
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

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

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692 **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 <u>congenital anomalies</u> (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 <u>miscarriage</u> (moderate quality evidence), <u>premature birth</u> (high quality evidence) and <u>low birth weight</u> (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 <u>premature birth</u> and <u>low birth weight</u> (high quality evidence).

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Who needs specific cardiac surveillance during pregnancy? <i>Based on IGHG cardiomyopathy guideline</i> ⁴³
<u>Cardiomyopathy surveillance</u> 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) ⁴³ .
No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal left ventricular systolic function immediately prior to or during the first trimester of pregnancy (moderate level recommendation, low quality evidence) ⁴³ .

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

- Risks of medical and elective termination of pregnancy following CAYCA cancer, 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

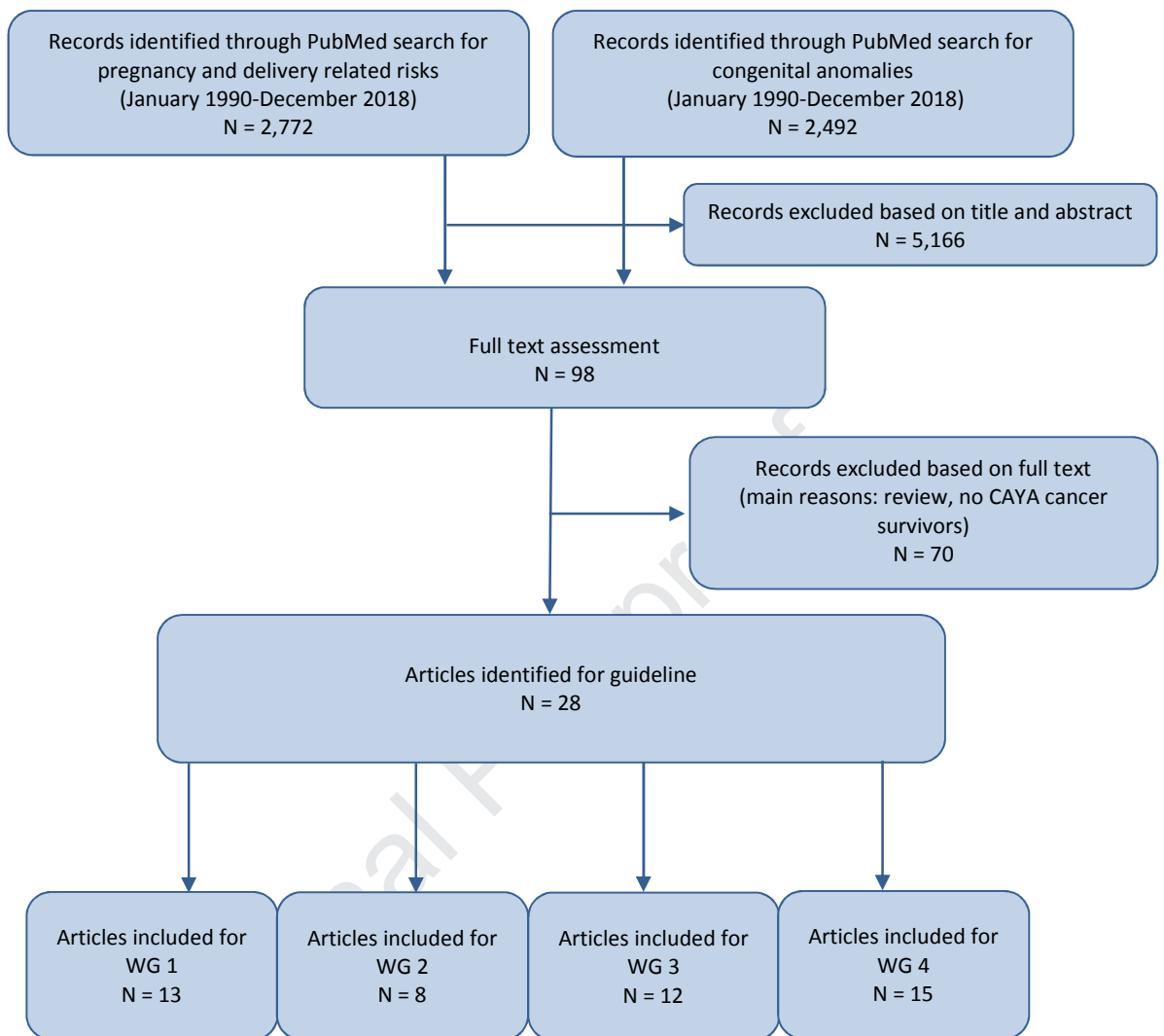


Figure 1. Flowchart of selected studies. Articles could be included for multiple working groups (WG).

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.