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W van Dorp, R Haupt, RA Anderson, RL Mulder, MM van den Heuvel-Eibrink, E van Dulmen-den Broeder, HI Su, Jeanette Falck Winther, MM Hudson, JM Levine*, WH Wallace*

*contributed equally

Author affiliations:

Wendy van Dorp, Department of Gynaecology and Obstetrics, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, The Netherlands.

Riccardo Haupt, Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

Richard A. Anderson, MRC Centre for Reproductive Health, Queens Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom.

Renee L. Mulder, Department of Paediatric Oncology, Emma Children's Hospital and Academic Medical Centre, Amsterdam, Netherlands.

Marry M. van den Heuvel-Eibrink, Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands.

Eline van Dulmen-den Broeder, Department of Paediatrics, Division of Paediatric Oncology/Haematology, VU University Medical Center Amsterdam, The Netherlands.

H. Irene Su, Department of Reproductive Medicine , Moores Cancer Center, University of California , San Diego , CA , USA.

Jeanette Falck Winther, Survivorship Unit, Danish Cancer Society Research Center , Copenhagen, and Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

Melissa M. Hudson, Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

Jennifer M. Levine, Division of Pediatric Hematology and Oncology, Weill Cornell Medicine, New York.

W. Hamish Wallace, Department of Paediatric Haematology & Oncology, Royal Hospital for Sick Children & The University of Edinburgh, Edinburgh, UK.

Corresponding author:

Wendy van Dorp

Department of Gynaecology and Obstetrics, Erasmus MC-University Medical Centre Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands. Electronic address: w.vandorp@erasmusmc.nl

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ABSTRACT

It is known that some survivors of childhood, adolescent and young adult cancer are at increased risk of gonadal dysfunction and adverse pregnancy outcomes. We reviewed currently available literature evaluating reproductive function and pregnancy outcomes of female cancer survivors diagnosed before the age of 25. High dose alkylating agent chemotherapy and abdominal/pelvic radiotherapy adversely impact gonadal function in a dose-related fashion, with older age at exposure conferring greater risk due to the age-related decline in ovarian reserve. Gonadal injury clinically manifests as ovarian hormone insufficiency (delayed or arrested puberty, premature ovarian insufficiency, or premature menopause) and infertility. The effect of molecular-targeted agents on ovarian function has not been established. For female survivors who maintain fertility, overall pregnancy (relative risk 0.67-0.81) and live birth rates (hazard ratio 0.79-0.82) are lower than those in the general public. Pregnancy in survivors of cancer may also be associated with risks to both the mother and fetus, related to miscarriage, preterm birth, and, rarely, cardiomyopathy. Women at risk for these complications require pre-conception assessment and counseling by both obstetricians and oncology providers. The risk for inherited genetic disease in offspring conceived after cancer treatment exposure is not increased. Optimizing reproductive outcomes and minimizing risks of pregnancy complications in survivors requires informed risk-based assessment and monitoring.

Introduction

The childhood cancer survivor population has been growing rapidly over the last four decades with five-year survival rates now approximately 80% in the developed world. Despite increasing survival, the majority of these survivors will experience at least one and often several chronic health conditions by age 40 years that will significantly impact on their overall quality of life[1,2]. Among the health consequences of cancer, gonadal dysfunction and infertility are major concerns of survivors and their parents, resulting in distress, fear, anxiety and interference with intimate relationships[3]. Identifying risk factors that impact on reproductive function and fertility is important to facilitate accurate counseling and timely referral for established (e.g. oocyte and embryo cryopreservation) and experimental (e.g. ovarian tissue cryopreservation) interventions that may help to restore future fertility in high-risk populations (reviewed elsewhere[4]). In this review, we assess currently available literature evaluating reproductive function and pregnancy outcomes of female childhood, adolescent and young adult cancer survivors diagnosed before the age of 25.

Cancer therapy and gonadal function

It is well established that some survivors are at increased risk of damage to reproductive function, which may manifest as ovarian hormone insufficiency (absent or arrested puberty, premature ovarian insufficiency (POI), also referred to as early menopause) and infertility[4]. POI was defined as a clinical condition that developed in any adult female at age < 40 years, characterized by the absence of menstrual cycles for ≥ 4 months and two elevated serum follicle-stimulating hormone levels in the menopausal range[5]. Compared to siblings, the risk of nonsurgical POI is increased, with a cumulative incidence of approximately 8-10% by age 40 years[6-8]. These manifestations generally reflect direct or indirect adverse effects of cancer treatment on the non-renewable pool of primordial follicles within the ovary[9].

The body of evidence describing adverse effects of multi-modal cancer therapies on female reproductive function is largely based on retrospective cohort studies[10]. Dissecting the contribution of individual therapeutic components in these studies is often difficult but increasingly data are available that elucidate predisposing treatments. These studies confirm that amongst chemotherapeutic agents, the alkylating agents impart higher risk, in a dose-related manner when both individual agents and combination of alkylating agents are used[11]. Importantly, there appears to be no consistent threshold for a safe alkylating agent dose.

The ovaries may also be damaged by radiation to a field that potentially exposes the ovaries (e.g., total body/abdominal/pelvic/spinal irradiation). The magnitude of the effect is related to the dose, fractionation schedule and age at the time of treatment. The oocyte is extremely sensitive to radiation with <2 Gray representing the estimated dose required to destroy 50% of primordial follicles[12]; normograms identifying the dose likely to cause POI across a range of ages have been produced[4].

Molecular-targeted agents such as monoclonal antibodies and kinase inhibitors are increasingly used in the treatment of female cancer. At present, the effects of such agents on female reproductive function are largely unknown, but there have been reports proposing a likely transient effect of bevacizumab (an anti-VEGF agent) on ovarian function[13]. As follicle growth is dependent on angiogenesis, normal folliculogenesis may be impaired by this agent; effects on the non-growing ovarian follicle pool remain unknown. Other agents may have effects on the non-growing primordial follicle pool through activity on pathways of physiological relevance to the control of follicle dormancy and growth activation. One potential example of this is imatinib, which has been reported to have adverse effects on ovarian function[14] but may also have protective effects against the gonadotoxicity of cisplatin[15]. The effect of 131I-metaiodobenzylguanidine for neuroblastoma is unclear, since only two cases have been reported resulting in damage to the female gonads, but because of the localisation of the tumours (pelvis) the ovaries might have received some scattered irradiation[16].

Diagnosing Premature Ovarian Insufficiency
POI, in addition to compromising fertility, is associated with osteoporosis, cardiovascular diseases, impaired well-being and compromised sexual health[5,17]. Therefore, surveillance of at risk survivors may facilitate early detection and access to interventions that preserve health and improve quality of life[18,19].

Several initiatives have developed national guidelines for POI surveillance in survivors[20-23]. However, many differences were observed, resulting in difficulties in implementing guidelines in clinical practice. As part of a larger international effort to harmonize existing late effects screening recommendations for survivors of childhood cancer, POI surveillance recommendations for female survivors were reviewed[19]. In Figure 1, the harmonized recommendations are shown. Gaps in knowledge were also identified, including the lack of information on safe treatment dosages and the role of genetic susceptibility on subsequent POI risk, to lead future directions in research.

Assessment for POI should begin, as appropriate for age, with documentation of pubertal, menstrual and pregnancy history and symptoms (e.g. hot flashes) and physical findings of ovarian hormone insufficiency (e.g. delayed/stalled puberty). Amongst useful biomarkers, FSH remains the key hormone of diagnostic value for POI but there are now increasing data on the value of AMH in identifying those women with low ovarian reserve following cancer therapy[24]. The value of AMH in predicting early menopause remains uncertain, and it is also important to recognise that a very low AMH does not preclude natural conception. Thus while this biomarker is of great value in a research context, its value in routine clinical practice is less clear. Antral follicle count by transvaginal ultrasound is also an established method for assessing ovarian reserve in adult women, but is not part of the definition of POI.

Treatment of ovarian hormone insufficiency

Sex steroid replacement therapy (SSRT) can remediate or prevent the consequences of estrogen deprivation in survivors with POI. SSRT differs for survivors who are pre-pubertal and those who experience POI after secondary sexual characteristics have developed. Timing and tempo of estrogen substitution in the pre-pubertal patient are crucial to ensure normal pubertal development (especially breast development) and an acceptable final height and ideally should be managed by a provider with expertise in paediatric pubertal development. In post-pubertal females, SSRT promotes bone and cardiovascular health[25]. Progesterone therapy is also needed to avoid endometrial hyperplasia and cancer in women with a uterus once breast development is complete.

In non-cancer survivors, POI is treated with SSRT to remediate symptoms of low estrogen. Moreover, women should be advised that SSRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection[5]. In these women, SSRT use before the age at natural menopause has not been found to increase the risk of breast cancer[5]. Unfortunately, literature on the effects of SSRT in female cancer survivors is scarce. Similarly there are limited data on oral versus transdermal administration. A crossover study of oral versus transdermal SSRT in young women with POI related to Turner syndrome and childhood cancer treatment showed that transdermal treatment is more effective than standard oral treatment in terms of bone health and cardiovascular health [26-28]. Numbers are limited and study groups heterogeneous, which emphasizes the importance of pursuing randomized studies evaluating SSRT in survivors.

While most providers would uniformly recommend SSRT to support pubertal development and growth, use of SSRT in older patients is variable, in part due to concerns about induction of second malignant neoplasms, especially breast cancer. In this regard, recent research from the Childhood Cancer Survivor Study reported that survivors with POI treated with SSRT have a lower risk of breast cancer compared to those who continue to menstruate naturally. These data suggest that SSRT does not affect breast cancer risk to same degree as endogenous hormones[29].

Pregnancy Rates

For survivors of reproductive-age, concerns about achieving pregnancy, maternal health during pregnancy and pregnancy outcomes represent priority health concerns. Large cohort studies have demonstrated that overall, female cancer survivors have lower rates of pregnancy[30-32] and live births[32-35] compared to sibling and general population controls (see Table 1). Risks for lowest rates occur following exposure to cranial and abdominal radiation. Abdominal radiotherapy is also associated with delayed time to pregnancy[36] and in a large German cohort of Hodgkin lymphoma survivors, pelvic radiotherapy was the key determinant of not achieving parenthood[37]. Pelvic radiotherapy may also affect the uterus with consequences for early and late pregnancy loss, and pregnancy complications (discussed below).

Chow et al demonstrated that survivors who received chemotherapy alone had lower live birth rates with HR 0.82 (confidence interval 0.76 to 0.89)[32]. Cyclophosphamide equivalent dose was associated at the highest doses with lower live birth rates (upper quartile vs no exposure: HR 0.85, confidence interval 0.74-0.98). Detailed information on treatment revealed that only busulfan and lomustine were identified as specific agents associated with reduced chance of pregnancy. This study also highlighted the impact of delaying pregnancy such that the effect of chemotherapy was magnified in women whose first pregnancy was after 30 years of age; thus there seems to be some evidence of age-related loss of fertility. This has clear implications for advising young women about the timing of pregnancy after cancer treatment. Higher pregnancy rates have been reported in more recent treatment eras, likely reflecting risk-adapted use of gonadotoxic treatment modalities[35].

It is important to note that pregnancy rates are not synonymous with either fertility or infertility. In the former, factors other than treatment exposure can affect pregnancy such as having a partner and the desire for having children. In addition, the presence of clinical infertility does not necessarily preclude pregnancy, especially with the use of assisted reproduction[36].

Pregnancy Outcomes

As in the general population, live birth rates in survivors are lower than pregnancy rates reflecting losses during pregnancy[32]. Cohort and national registry data show that spontaneous pregnancy loss <22 weeks of gestation occurs with limited frequency (7-15%) in survivors, comparable in rate to sibling and population controls[38-40]. However higher spontaneous pregnancy loss rates have been reported in women exposed to cranial radiation (1.4- to 6.1-fold increase) and abdomino-pelvic radiation (1.4- to 2.8-fold increase)[33,38,39]. Of particular concern is the observation that second-trimester losses are significantly increased in women with these exposures[33,39]. Abdomino-pelvic radiation is hypothesized to damage the endometrium, myometrium, or uterine vessels[41-43]. Preterm birth <37 weeks gestation poses significant risks to offspring and occurs in 13-21% of pregnancies in survivors[44,45]. Compared to siblings or the general population, these rates are 1.5- to 2-fold higher in survivors, including similarly elevated relative risks for early preterm births prior to 32 weeks[44-47]. Preterm birth risk is related to abdomino-pelvic radiation in a dose-dependent fashion, but does not appear to vary by radiation before or after menarche[33,39,44]. Most data report no association between preterm birth and exposure to alkylating chemotherapy[33,44]. There is a dearth of data on risks of very early preterm birth (<28 weeks), as well as causes for preterm birth, i.e. spontaneous versus iatrogenic. Hence, there remains a lack of studies on how to prevent this adverse late effect.

Concordant with higher rates of preterm birth, low birth weight babies (<2500 grams) occur in 7-15% of offspring of cancer survivors, which is 2- to 3-fold more frequently than in the offspring of controls[39,44,45,48]. With the exception of abdomino-pelvic radiation, higher rates of offspring being small for gestational age are not observed, suggesting that most of low birth weight risk is attributable to preterm birth rather than intrauterine growth restriction[44,45,49]. Overall, cancer survivors do not appear to be at higher risk of stillbirth when compared to the general population[38,47]. However, similar to other pregnancy outcomes, abdomino-pelvic radiation exposure may be associated with higher perinatal death risk, but studies are limited in power due to overall low incidence[33,50-52].

Cancer treatment exposures including anthracyclines, chest radiation, and molecular-targeted agents pose cardiovascular risks that can impact pregnancy outcomes. Several cohort studies report approximately 5% absolute risk of pre-eclampsia during pregnancy in cancer survivors, but rates are

not higher or only modestly (1.4-fold) higher than in controls[45,53,54]. In the British Childhood Cancer Survivor Study, survivors of Wilms tumor treated with abdominal radiotherapy were at a threefold risk for the development of hypertension during pregnancy. Pregnancy-associated cardiomyopathy occurred rarely (0.3%) in a retrospective cohort study of 847 survivors, but increased risk was observed with anthracycline exposure[55]. Hence, the International Late Effects of Childhood Cancer Guideline Harmonization Group recommends that cardiomyopathy surveillance is reasonable before pregnancy or in the first trimester for all female survivors treated with anthracyclines or chest radiation[56]. With increased use of targeted therapy, long-term and pregnancy-related cardiotoxicity of these agents requires further study.

During pregnancy, overall rates of gestational diabetes are low (<5%) and are not consistently higher in cancer survivors than controls[45,54]. However, abdominal radiation has been associated with a 2.7 to 4.7-fold higher risk in one study[33]. Cesarean deliveries are consistently 1.2 to 2.3-fold higher in survivors than controls[45,54].

Because of these potential pregnancy-related complications, survivors would benefit from preconception counseling to estimate magnitude of risk, establish a surveillance plan, and discuss interventions to reduce risk; obstetricians and oncology providers need to be aware of these complications to co-manage survivors accordingly (see Figure 2). There is a dearth of intervention studies focused on improving these adverse perinatal outcomes. Moreover, these data were derived from cohorts treated with regimens that may no longer be in practice and may be less applicable for counseling patients treated with more contemporary treatment strategies.

Health risks in offspring
Childhood cancer survivors represent one of the largest groups of people exposed to well-documented high doses of potent mutagens, in the form of chemotherapy and radiation therapy, that might affect human germ cells, and cause potential transmissibility of germline damage to offspring[57]. Health indicators of a possible mutagenic effect of cancer therapy that have been considered include single gene disorders and chromosomal abnormalities (rare but purely genetic diseases), the relatively common congenital malformations (which, although to some extent genetically determined, are multifactorial) as well as miscarriage, stillbirths and perinatal death. The occurrence of cancer and sex ratio alterations have also been considered as appropriate measures of germ-cell mutations in the next generation. Although most early studies lacked sufficient statistical

power, their findings suggest a low risk of treatment-induced heritable genetic effects. Findings of more recent, larger and refined studies are shown in Table 2.

Five population-based Nordic studies evaluating the risk of sex-ratio[58], congenital malformations[59,60], chromosomal abnormalities[61], and hospitalizations[62] in offspring of survivors did not observe a significantly increased risk. In the largest population-based study to date that evaluated cancer risk in the next generation, 9877 children born to survivors showed no increased risk of cancer except in the rare event of a familial cancer syndrome[63].A population-based cohort study from the BCCS reporting on sex ratio alterations[64] maximized the statistical power by pooling their data with those from previous large-scale studies[58]. The sex ratio of the offspring of survivors treated with potentially high-dose gonadal irradiation was not significantly different from that of survivors treated with presumably low-dose gonadal irradiation (OR 0.92; 0.78–1.08). These findings were confirmed by more recent studies in the USA[45] and Western Australia[54].

Although the design and methodology differed between the more recently published studies on the risk of congenital malformations in the offspring, no significantly increased risks have been reported[45,46,51,54,59,60]. Two comprehensive studies evaluated the risk of genetic disease in children of childhood cancer survivors[65,66]. Strong evidence was provided that potentially mutagenic chemotherapy and radiotherapy doses to the ovaries were not associated with genetic defects in the children. Consistent with the epidemiological studies, no evidence for an increased rate of germline minisatellite mutations at hypervariable loci, markers for radiation-induced human germline mutation, was identified in parents who had received radiotherapy[67].

To date, no environmental exposure including cancer therapy has been proven to cause human germ line mutations that manifest as heritable disease in the offspring[57]. It has been suggested that inadequate study size, but also failure to measure the appropriate outcome might explain the reassuring results reported in the vast majority of studies on health risks in offspring[57]. Total genomic sequencing directly evaluating the presence of genetic damage in germ cells and epigenomic analysis might be a way forward to address this issue in the future particularly in the era of targeted cancer therapies that include epigenetic modifiers[68].

Conclusion

Over the last decades, the adverse effects of cancer and its therapy on reproductive outcomes have become clear, especially after specific treatment. Yet, significant gaps in knowledge continue to limit the ability to assess risk for gonadal failure in individual patients receiving these therapies. Little is

known about how host factors such as genetic risks for infertility or differences in drug metabolism affect risk from treatment. The impact of newer (molecular-targeted) agents is virtually unknown. And, once therapy is delivered and a gonadotoxic insult has occurred, we know little about whether there is compensation in the rate of decline of ovarian reserve. Furthermore, the methods by which we assess impending ovarian insufficiency and loss of the reproductive window still remain extremely inexact, limiting the ability to counsel survivors about making reproductive decisions.

We recommend that all clinical trials and treatment strategies for with cancer include surveillance for adverse effects on reproductive health, which in female patients should include assessment of ovarian function, pregnancy outcomes and fertility (Figure 2). Detailed information about chemotherapy and radiotherapy exposures should routinely be collected to correlate with reproductive outcomes as treatment exposures rather than the nature of the cancer largely determines risks for chronic health conditions, including gonadal function and fertility in cancer survivors. Survivors should receive personalized counselling about type and magnitude of reproductive health risks based on their specific treatment exposure and studies should be established to determine the efficacy of fertility preservation procedures that are undertaken in this population.

While oncofertility options have expanded globally, there still exists a need to identify the specific fertility threats related to the primary cancer and treatment patterns by country. Woodruff et al proposed a global oncofertility index to permit experts to determine the scale of the problem and facilitate the development of educational tools that define access to reproductive technologies[69]. As identified in the IGHG POI guideline, there are major gaps in knowledge, such as the lack of information about safe treatment dosages, safety of novel therapies, and the role of genetic susceptibility on subsequent POI risk in survivors[19].

Figure 1: Harmonized recommendations for POI surveillance in survivors of childhood, adolescent and young adult cancer.

Premature ovarian insufficiency (POI) is defined as a clinical condition developing in any adult female before age 40 years that is characterized by the absence of menses for >4 months and two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (on the basis of the maximum threshold of the laboratory assay used). *Treatments with evidence of causing POI include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy to a field that includes the ovaries (level A evidence). †At least annually, with increasing frequency as clinically indicated based on growth and pubertal progression. ‡At least for girls of 11 years of age and older, and for girls with primary amenorrhoea (age 16). §If amenorrhoea, measure FSH and oestradiol randomly; if oligomenorrhoea, measure during early follicular phase (day 2-5). This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after two months without oral contraceptive pills. ¶The absence of initiation of puberty (Tanner stage 2 breast development) in girls 13 years or older or failure to progress in pubertal stage for ≥ 12 months. AMH, anti-Müllerian hormone; CAYA, childhood, adolescent, and young adult; Level A, high level of evidence; Level B, moderate/low level of evidence; Level C, very low level of evidence[19].

General recommendation

Survivors treated with one or more potentially gonadotoxic treatments*, and their providers, should be aware of the risk of premature ovarian insufficiency and its implications for future fertility (level A and level C evidence).

Who needs surveillance?

Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility *is recommended* for survivors treated with:
- Alkylating agents in general (level A evidence)
- Cyclophosphamide and procarbazine (level C evidence)
- Radiotherapy potentially exposing the ovaries (level A evidence)

What surveillance modality should be used for pre- and peri-pubertal survivors?

Monitoring of growth (height) and pubertal development and progression (Tanner stage) *is recommended* for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search).*†

FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who fail to initiate or progress through puberty (expert opinion/no literature search).*‡

What surveillance modality should be used for post-pubertal survivors?

A detailed history and physical examination with specific attention for premature ovarian insufficiency symptoms, e.g. amenorrhoea and irregular cycles *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion/no literature search).*

FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility. Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable (expert opinion/no studies).§‖

AMH *is not recommended* as the *primary surveillance modality* for evaluation of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who desire assessment about potential future fertility (expert opinion/no studies).

AMH *may be reasonable* in conjunction with FSH and oestradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* aged ≥25 years who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility (expert opinion/no studies).

When should pre- and peri-pubertal survivors be referred?

Referral to paediatric endocrinology / gynaecology *is recommended* for any survivor who has
- No signs of puberty by 13 years of age.
- Primary amenorrhoea by 16 years of age.
- Failure of pubertal progression.¶
  (expert opinion/no literature search)

When should post-pubertal survivors be referred?

Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries* who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency (expert opinion/no literature search).

What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?

Consideration of sex steroid replacement therapy *is recommended* for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency *by referral to gynaecology/endocrinology* (expert opinion/no literature search).

What should be done when potential for future fertility is questioned?

Referral to gynaecology / reproductive medicine / endocrinology (according to local referral pathways) *is recommended* for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or ovarian irradiation* without signs and symptoms of premature ovarian insufficiency who desire assessment about potential for future fertility (expert opinion/no literature search).

Table 1: Pregnancy and Live Birth Rates in Childhood Cancer Survivors.

Author, year	Study Cohort (n=)	Treatment period	Age at diagnosis	Control group	Pregnancy Rates	Live Birth Rates	Risk estimate
Green 2009[30]	CCSS (n=5149)	1970-1986	0-21 years	Sibling controls	RR 0.81 (0.73-0.90)	Not reported	Hypothalamic/pituitary radiation dose > or = 30 Gy (RR, 0.61; 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant
Reulen 2009[33]	BCCSS (n=10,483)	1940-1991	0-14 years	General population England and Wales	Not reported	O/E 0.64 (0.62-0.66)	Brain and abdominal RT
Stensheim 2011[31]	Cancer Registry of Norway (n=16,105)	1967-2004	16-25 years (subset of total study)	General population	HR 0.67 (0.63-0.73)	Not reported	Not applicable as risks reported for total cohort (age 16-45)
Pivetta 2011[34]	Italian AIEOP Off-Therapy Registry (n=2,670)	1960-1998	0-14 years	General Population	Not reported	O/E 0.57 (95th 0.53-0.62)	Malignancy of the CNS
Chow 2016[32]	CCSS, chemotherapy only (n=5,298)	1970-1986	0-21 years	Siblings	HR 0.87 (0.81-0.94; p<0.0001)	HR 0.82, (0.76–0.89; p<0.0001)	Busulfan, higher doses of lomustine (≥411mg/m^2) and cyclophosphamide equivalent doses in the upper quartile (≥11 295 mg/m^2).
Armuand 2017[35]	Swedish National Patient Register (n=552)	Patients **born** between 1973-1977	0-21 years	Age matched controls from the general population	Not reported	HR0.79 before 1988 HR 0.71 after 1988 0.90	Malignancy of the eye, CNS or leukemia

CCSS=Childhood Cancer Survivor Study, Gy=Gray, RR=relative risk, CI=confidence interval, BCCSS=British Childhood Cancer Survivor Study, O/E=Observed/Expected, RT=radiotherapy, AIEOP=Italian Pediatric Ematology and Oncology Association, CNS=central nervous system, HR=hazard ratio.

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Table 2: Health risk outcomes in cancer survivor offspring[1].

Reference	Study cohort	Offspring (no.), (CS no.)	Outcome	Comparison	Cancer (treatment)	Health risk outcomes measures	Risk estimate (95% CI)
Chiarelli 2000 [51]	Female CCS - Ontario Cancer Registry, diagnosis < 20 yr (1964–1988)	594 singleton pregnancies (340 survivors)	Questionnaire	Internal comparison: Patients treated with non-sterilizing surgery only or no treatment	Medical records. 5 treatment groups: non-sterilizing surgery; AA; AP irradiation: low ≤ 25 Gy, high > 25 Gy; AA plus AP irradiation; and all other treatments	Congenital malformations (22 cases)	-CS with AP irradiation: OR 0.45 (0.12-1.70) -General: decreased risk of having an infant with a congenital anomaly compared with those having surgery only -No effect of high dose *vs* low dose AP radiation (small no.)
Winther 2003 [58]	CCS - Danish Cancer Registry, diagnosis <20 yr (1943–1996)	2130 offspring (born to 550 female and 550 male survivors)	Registry linkage	General Danish Population Internal comparisons	Registry-based information on radiotherapy (yes/no) 5 categories of estimated radiation dose to gonads: low/ low-medium/ medium/ medium-high/ high	Sex ratio alterations (2130 offspring)	-male (0.99): female (1.00) ratio *vs* Danish population (1.06) -no effect of RT on the M:F ratio -*p* for trend with ovarian dose = 0.51
Winther 2004 [61]	CCS - Danish Cancer Registry, diagnosis < 20 yr (1943–1996)	2630 offspring (4676 female and male survivors)	Registry linkage	Offspring of siblings	Registry-based information on RT (yes/no) Information on CT abstracted from medical records (for survivors with affected outcomes only)	Chromosomal abnormalities (8 survivors with ≥1 child/ fetus with an abnormal karyotype)	Proportion of live-born children with abnormal karyotypes born to CS : 0.21% and siblings 0.21% Direct comparison with siblings' offspring: Down syndrome (RR 1.07; 95% CI, 0.16–5.47), Turner syndrome (RR, 1.32; 95% CI, 0.17–7.96).
Reulen 2007 [64]	BCCSS - National Registry of Childhood Tumours, diagnosis < 15	6232 offspring (born to 3218 female and male survivors)	Questionnaire obtained from general practitioners	General population of England and Wales Internal comparisons among female CCS:	Registry-based information on RT (yes/no) and CT (yes/no). High *vs* low estimated RT dose to gonads	Sex ratio alterations (6232 offspring)	-M:F ratio CCS offspring *vs* general population: 1.08 (1.01-1.15) *vs* 1.05 -RT only *vs* no RT and CT: OR 0.97 (0.81-1.16)

				-CCS without CT/RT -High *vs* low gonadal dose			-CT only *vs* no RT and CT OR 1.00 (0.77-1.30) -High-dose *vs* low dose gonadal RT OR 0.95 (0.77-1.18)
Mag elsse n 2008 [46]	CS – Norway, diagnosis 15-35 yr (1980–1997)	First-born offspring (number not stated) (born to 251 female CS and 487 male CS)	Registry information	First-born offspring in the general population of Norway	Hospital-based information on cancer treatment 4 categories: surgery alone, RT (+/- surgery), CT (+/-surgery), and RT and CT (+/-surgery) (not included in analyses for malformation outcome)	Congenital malformations (7 cases)	OR 0.7 (0.4-1.6) in female CS
Wint her 2009 [59]	CCS - Danish Cancer Registry, diagnosis <20 yr (1950–1996)	1715 offspring (born to 970 survivors)	Registry linkage	Offspring of siblings	-Registry-based information on on RT (yes/no) -4 categories of estimated RT dose to ovary and uterus: low/ low-medium/ medium-high/ high	Congenital malformations (44 cases at birth; 96 cases later in life)	Prevalence proportion ratio at birth, survivors' *vs* siblings' offspring: 1.1 (0.8–1.5) or *versus* general Danish population Observed-to-expected ratio, 1.2 (0.9–1.6) Offspring of irradiated vs non-irradiated parents (PPR, 1.2 *vs* 1.0 at birth) Including malformations diagnosed later in life no ratio change
Muel ler 2009 [45]	CS - Seattle, Utah, Detroit and Atlanta, USA, diagnosis <20 yr (1973–2000)	1898 first live births (born to 898 CS; 892 CCS; 1006 adolescent cervical and genital CS)	Registry linkage	Comparison subjects selected from birth records	Registry-based information on cancer therapy 4 categories: CT, surgery, RT, and combinations	Congenital malformations (10 cases) Sex ratio alterations (1898 offspring)	-RR 0.92 (0.48-1.75) -M:F ratio among offspring in the two cohorts and comparisons were similar, ranging from 0.98 to 1.02 -CCS: RR 1.00 (0.93-1.07) -Adolescent cervical and genital CS: RR, 0.97 (0.90-1.03) -No significant increased RRs for malformations across groups
Mad	CS - Finnish	-26331 offspring	Registry	-Population	Registry-based information on RT	Cancer (65 cases in	-Offspring of CS: SIR 1.67 (1.29-

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anat-Harjuoja 2010 [63]	Cancer Registry, diagnosis <35 yr (1953–2004)	of 12735 survivor parents -9877 children born after their parent's diagnosis (4764 female and 5113 male CS)	linkage	expectations based on cancer incidence rates in Finland (SIR) -Indirect comparison with offspring of siblings	(yes/no)	children born after their parent's diagnosis)	2.12) -Offspring of CS, excluding hereditary cases: SIR 1.03 (0.74-1.40) -Offspring of siblings: SIR, 1.07 (0.94-1.21) - RT no effect on the risk (SIR, 0.91 (0.51-1.49)
Green 2010 [70]	National Wilms Tumor LTFUS: Female CCS (and partners of male CS of Wilms tumor) (<Jan 2007)	1021 pregnancies of ≥ 20 weeks' duration, including 955 liveborn singletons; 677 included in analyses (2369 female CS and partners of 2060 male CS of Wilms tumor)	Self-administered questionnaire	Internal comparison	-RT doses estimated on basis of RT treatment protocols, and each patient assigned a flank irradiation dose category except for those who received whole-abdomen irradiation -5 dose categories in Gy	Congenital malformations (44 cases)	p for trend with radiation dose = 0.94
Winther 2010 [62]	CCS - Danish Cancer Registry, diagnosis <20 yr (1950–1996)	1920 offspring (born to 527 female and 539 male CS)	Registry linkage	Offspring of siblings Population-based comparisons	Registry-based information on RT (yes/no) 4 categories of estimated RT dose to ovary, uterus and pituitary gland: low/ low-medium/ medium-high/ high	Untoward disorders measured as hospitalization in childhood assuming that hospitalization is an indicator of multifactorial genetic disease (1053 discharge diagnoses in CS' offspring)	HR ratios compared to population comparison: CS' offspring: HHR, 1.05 (95% CI, 0.98–1.12) siblings' offspring: 1.01 (95% CI, 0.971.05) HRR irradiated parents vs non-irradiated parents based on population comparisons (1.1 vs 1.0) but unrelated to estimated radiation dose to gonads A 6-fold excess risk for hospitalization for malignant tumors in the offspring of survivors largely explained by hereditary cancer syndromes
Wint	CS - Danish	472 CS ; 145 case	Registry	-Internal comparison:	Medical records, including	Genetic diseases	Dose–response findings:

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her 2012 [66]	Cancer Registry, diagnosis <20yr (1943–1996)	CS (with affected child or stillbirth) and 372 sub-cohort members (including 45 cases) (1/3 of a fertility cohort consisting of 1474 CS with 2767 pregnancies included in the above case-cohort study)	linkage	Non-irradiated survivors (for association with RT overall and for association with ovarian and uterus and testicular dose) -Non-exposed to CT (for association with CT overall)	detailed information on chemotherapy and individual preconception RT doses to ovaries, uterus and pituitary gland	defined as chromosomal abnormalities, congenital malformations, stillbirths, and neonatal deaths (181 presumed genetic diseases in offspring)	RRs for ovarian RT dose categories >0 to < 0.50 Gy and ≥ 0.50 Gy (with non-irradiated being reference): 1.12 and 1.04, respectively (p = 0.96) Risk of genetic disease among children of CS: -Irradiated *versus* non-irradiated CS: RR, 1.02 (0.59-1.44; p = 0.94) -AA *vs* no AA agents in CS: RR, 0.82 (0.53-1.28; p = 0.51) -An association between uterine dose and congenital malformations, stillbirths, and neonatal death, taken together, was of borderline statistical significance (p = 0.07) with the highest uterine doses associated with a 2.3-fold increased risk (ns)
Sign orell o 2012 [65]	CCSS - Canada/USA, diagnosis <21 yr (1970–1986)	4699 offspring (born to 1627 female and 1128 male CS)	Self-administered questionnaire	Internal comparison Non-irradiated CS (for association with RT dose) Non-exposed to CT (for association with CT)	Medical records, including AAD score: 1-3 (lowest, middle and top tertile exposure) and individual preconception RT doses to the gonads	Congenital anomalies defined as cytogenetic abnormalities, single-gene defects, and congenital malformations(129 offspring with congenital anomalies)	-Dose–response findings: ORs for ovarian RT dose categories low, medium, and high 0.87, 0.80, 0.59 respectively (p for trend with radiation dose = 0.53) -ORs for AAD scores categories lowest, middle, and top tertile exposure were 0.63, 1.00, and 1.13 (p for trend with AAD score = 0.69) For congenital malformations, ORs for ovarian radiation dose categories ranged from 0.84 to 1.14, suggesting no adverse effect. AAD score analysis showed a non-significantly

							decreased risk for the lowest and non-significantly increased risks for the middle and top tertile exposure
Hagg ar 2014 [54]	CS -Western Australia Cancer Registry, diagnosis 15-39 yr (1982–2007)	1894 first completed pregnancies (1894 female CS)	Registry linkage	Population-based comparisons without cancer	5 treatment groups:, surgery only, CT only, RT only, CT and RT, and all other types and therapy combinations (not included in analyses for malformation outcome)	Congenital malformations (12 cases) Sex ratio alterations (1894 offspring)	RR 0.78 (0.41-1.37) M:F ratio: RR 1.05 (0.98-1.10)
Sepp anen 2016 [60]	CS - Finnish Cancer Registry, diagnosis < 35 yr (1953–2004)	6862 offspring; (born to 3929 CS; 2197 female and 1732 male CS) 2412 CCS offspring, 4450 offspring of young adult CS	Registry linkage	Offspring of siblings	Registry-based information on RT (yes/no)	Congenital malformations (220 cases)	Prevalence ratios CS' vs siblings' offspring: -Any anomaly: 1.17 (0.92–1.49) -Lip and palate anomalies:2.09 (1.06-4.12) - Any anomaly in offspring of retinoblastoma (3.15, 1.37-7.23), and renal tumours (2.13, 1.07-4.26)(small no.) -No association with RT of the parent (1.12, 0.86-1.45)

CCS=childhood cancer survivors, yr=years, AA=alkylating agents, AP=abdomino-pelvic, Gy=Gray, M:F=male:female, BCCSS=British Childhood Cancer Survivor Study, CS=cancer survivors, SIR=standardized incidence rates, LTFUS=long-term follow-up study, HR=hospitalization rate, CCSS=Childhood Cancer Survivor Study, AAD=alkylating agent dose, PR=prevalence ratio. [1] The following health risk outcomes measures miscarriage, stillbirth and perinatal death are evaluated in the section Pregnancy Outcomes, RT=radiotherapy, CT=chemotherapy.

Figure 2: Assessment of the postpubertal survivor
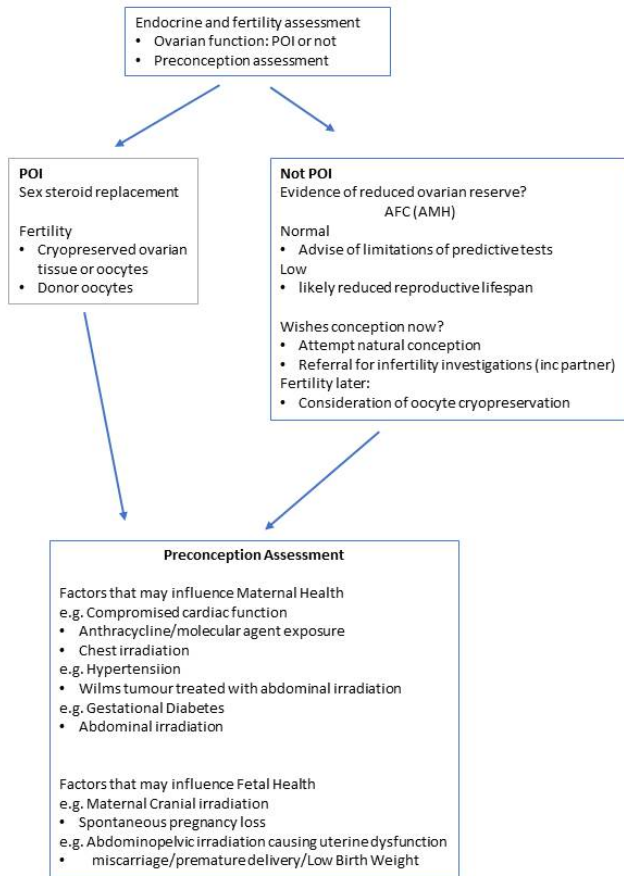
POI=premature ovarian insufficiency; AFC=antral follicle count; AMH= anti-Müllerian hormone.

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Assessment of the postpubertal survivor

Endocrine and fertility assessment
- Ovarian function: POI or not
- Preconception assessment

POI
Sex steroid replacement

Fertility
- Cryopreserved ovarian tissue or oocytes
- Donor oocytes

Not POI
Evidence of reduced ovarian reserve?
                    AFC (AMH)
Normal
- Advise of limitations of predictive tests
Low
- likely reduced reproductive lifespan

Wishes conception now?
- Attempt natural conception
- Referral for infertility investigations (inc partner)
Fertility later:
- Consideration of oocyte cryopreservation

Preconception Assessment

Factors that may influence Maternal Health
e.g. Compromised cardiac function
- Anthracycline/molecular agent exposure
- Chest irradiation
e.g. Hypertensiion
- Wilms tumour treated with abdominal irradiation
e.g. Gestational Diabetes
- Abdominal irradiation

Factors that may influence Fetal Health
e.g. Maternal Cranial irradiation
- Spontaneous pregnancy loss
e.g. Abdominopelvic irradiation causing uterine dysfunction
- miscarriage/premature delivery/Low Birth Weight