Reproductive function and outcomes in female survivors of childhood, adolescent and young adult cancer: a review

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Running title: Reproductive outcomes in female cancer survivors
**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. 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. 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). 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. 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. Compared to siblings, the risk of nonsurgical POI is increased, with a cumulative incidence of approximately 8-10% by age 40 years. These manifestations generally reflect direct or indirect adverse effects of cancer treatment on the non-renewable pool of primordial follicles within the ovary.

The body of evidence describing adverse effects of multi-modal cancer therapies on female reproductive function is largely based on retrospective cohort studies. 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. 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; normograms identifying the dose likely to cause POI across a range of ages have been produced.

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. 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 but may also have protective effects against the gonadotoxicity of cisplatin. The effect of 131I-metiodobenzylguanidine 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.

**Diagnosing Premature Ovarian Insufficiency**

POI, in addition to compromising fertility, is associated with osteoporosis, cardiovascular diseases, impaired well-being and compromised sexual health. Therefore, surveillance of at risk survivors may facilitate early detection and access to interventions that preserve health and improve quality of life.

Several initiatives have developed national guidelines for POI surveillance in survivors. 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. 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. 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. 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. In these women, SSRT use before the age at natural menopause has not been found to increase the risk of breast cancer. 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. 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 hormones29.

**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 pregnancy30-32 and live births32-35 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 pregnancy36 and in a large German cohort of Hodgkin lymphoma survivors, pelvic radiotherapy was the key determinant of not achieving parenthood37. 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 modalities35.

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 reproduction36.
Pregnancy Outcomes

As in the general population, live birth rates in survivors are lower than pregnancy rates reflecting losses during pregnancy.\(^\text{32}\) 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.\(^\text{38-40}\) 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)\(^\text{33,38,39}\). Of particular concern is the observation that second-trimester losses are significantly increased in women with these exposures\(^\text{33,39}\). Abdomino-pelvic radiation is hypothesized to damage the endometrium, myometrium, or uterine vessels\(^\text{41-43}\).

Preterm birth <37 weeks gestation poses significant risks to offspring and occurs in 13-21% of pregnancies in survivors.\(^\text{44,45}\) 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.\(^\text{46-47}\) 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.\(^\text{33,39,44}\) Most data report no association between preterm birth and exposure to alkylating chemotherapy\(^\text{33,44}\). 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.\(^\text{39,44,45,48}\). 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.\(^\text{44,45,46}\) Overall, cancer survivors do not appear to be at higher risk of stillbirth when compared to the general population.\(^\text{39,47}\). 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.\(^\text{33,45-52}\).

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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{45,54}. However, abdominal radiation has been associated with a 2.7 to 4.7-fold higher risk in one study\textsuperscript{33}. Cesarean deliveries are consistently 1.2 to 2.3-fold higher in survivors than controls\textsuperscript{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\textsuperscript{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\textsuperscript{58}, congenital malformations\textsuperscript{59,60}, chromosomal abnormalities\textsuperscript{61}, and hospitalizations\textsuperscript{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\textsuperscript{63}. A population-based cohort study from the BCSS reporting on sex ratio alterations\textsuperscript{64} maximized the statistical power by pooling their data with those from previous large-scale studies\textsuperscript{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\textsuperscript{55} and Western Australia\textsuperscript{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\textsuperscript{45,46,51,54,59,60}. Two comprehensive studies evaluated the risk of genetic disease in children of childhood cancer survivors\textsuperscript{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\textsuperscript{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\textsuperscript{67}. 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\textsuperscript{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\textsuperscript{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. 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.
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 12 months and two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (see the back of the maximum threshold of the laboratory assay used). *Treatments with evidence of causing POI include cytotoxic agents in general (level C evidence), and radiotherapy to a field that includes the ovaries (level IA 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 amenorrhea (age 16). §If amenorrhea, measure FSH and oestradiol randomly; if oligomenorrhea, measure during early follicular phase (day 2-4). This assessment should be performed after androgen contraceptive pill/dexa- steroid replacement therapy use, ideally after two months without exogenous hormone replacement. ¶The absence of induction of puberty ( Tanner stage 2- breast development) in girls 13 years of age or failure to progress in pubertal stage for 12 months. AMH, anti-Müllerian hormone; CAVA, childhood, adolescent, and young adult; level 1A, high level of evidence; level 1B, moderate level of evidence; level 1C, very low level of evidence.

<table>
<thead>
<tr>
<th>General recommendation</th>
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<tbody>
<tr>
<td>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).</td>
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<table>
<thead>
<tr>
<th>Who needs surveillance?</th>
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<tbody>
<tr>
<td>Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility is recommended for the woman treated with:</td>
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<tr>
<td>- All imaging in general (level C evidence)</td>
</tr>
<tr>
<td>- Cyclophosphamide and procarbazine (level C evidence)</td>
</tr>
<tr>
<td>- Radiotherapy potentially exposing the ovaries (level A evidence)</td>
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<tr>
<th>What surveillance modality should be used for pre- and peripubertal survivors?</th>
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<tr>
<td>Monitor rates of growth (height) and pubertal development and progression (Tanner stage) is recommended for pre- and peripubertal women treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries (level A evidence).</td>
</tr>
<tr>
<td>FSH and oestradiol are recommended for evaluation of premature ovarian insufficiency in pre-pubertal children treated with potentially gonadotoxic chemotherapy or radiotherapy potentially exposing the ovaries, who have failure of progression through pubertal stages or no breast development (level A evidence).</td>
</tr>
<tr>
<td>AMH is recommended for primary surveillance modality for evaluation of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries (expert opinion/no literature search).</td>
</tr>
<tr>
<td>AMH may be reasonable in combination with FSH and oestradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries, up to 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).</td>
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<table>
<thead>
<tr>
<th>What should pre- and peripubertal survivors be referred for?</th>
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<tbody>
<tr>
<td>Referral to gynaecology/endocrinology is recommended for any survivor who has</td>
</tr>
<tr>
<td>- No signs of puberty by 13 years of age.</td>
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<tr>
<td>- Primary amenorrhea by 16 years of age.</td>
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<tr>
<td>- Failure of pubertal progression (expert opinion/no literature search).</td>
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<thead>
<tr>
<th>What should post-pubertal survivors be referred for?</th>
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<tbody>
<tr>
<td>Referral to gynaecology/endocrinology is recommended for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or radiotherapy, potentially exposing the ovaries, who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency, and who desire assessment about potential for future fertility (expert opinion/no literature search).</td>
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<tr>
<th>What should be done when abnormalities are identified in pre- and post-pubertal survivors?</th>
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<tbody>
<tr>
<td>Consideration of oestrogen replacement therapy is recommended for pre-, post- and post-pubertal survivors diagnosed with premature ovarian insufficiency by referral to gynaecology/endocrinology (expert opinion/no literature search).</td>
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<tr>
<th>What should be done when potential for future fertility is questioned?</th>
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<tbody>
<tr>
<td>Referral to gynaecology/endocrinology is recommended for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or radiotherapy, without signs and symptoms of premature ovarian insufficiency who desire assessment about potential for future fertility (expert opinion/no literature search).</td>
</tr>
</tbody>
</table>
Table 1: Pregnancy and Live Birth Rates in Childhood Cancer Survivors.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Cohort (n=)</th>
<th>Treatment period</th>
<th>Age at diagnosis</th>
<th>Control group</th>
<th>Pregnancy Rates</th>
<th>Live Birth Rates</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green 2009\textsuperscript{a}</td>
<td>CCSS (n=5149)</td>
<td>1970-1986</td>
<td>0-21 years</td>
<td>Sibling controls</td>
<td>RR 0.81 (0.73-0.90)</td>
<td>Not reported</td>
<td>Hypothalamic/pituitary radiation dose &gt; or = 30 Gy (RR, 0.61; 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose greater than 5 Gy we're less likely to have ever been pregnant</td>
</tr>
<tr>
<td>Reulen 2009\textsuperscript{a}</td>
<td>BCSS (n=10,483)</td>
<td>1940-1991</td>
<td>0-14 years</td>
<td>General population England and Wales</td>
<td>Not reported</td>
<td>O/E 0.64 (0.62-0.66)</td>
<td>Brain and abdominal RT</td>
</tr>
<tr>
<td>Stensheim 2011\textsuperscript{a}</td>
<td>Cancer Registry of Norway (n=16,105)</td>
<td>1967-2004</td>
<td>16-25 years (subset of total study)</td>
<td>General population</td>
<td>HR 0.67 (0.63-0.73)</td>
<td>Not reported</td>
<td>Not applicable as risks reported for total cohort (age 16-45)</td>
</tr>
<tr>
<td>Pivetta 2011\textsuperscript{a}</td>
<td>Italian AIEOP Off-Therapy Registry (n=2,670)</td>
<td>1960-1998</td>
<td>0-14 years</td>
<td>General Population</td>
<td>Not reported</td>
<td>O/E 0.57 (95% 0.53-0.62)</td>
<td>Malignancy of the CNS</td>
</tr>
<tr>
<td>Chow 2016\textsuperscript{a}</td>
<td>CCSS, chemotherapy only (n=5,298)</td>
<td>1970-1986</td>
<td>0-21 years</td>
<td>Siblings</td>
<td>HR 0.87 (0.81-0.94; p&lt;0.0001)</td>
<td>HR 0.82 (0.76-0.89; p&lt;0.0001)</td>
<td>Busulfan, higher doses of lomustine (≥411mg/m\textsuperscript{2}) and cyclophosphamide equivalent doses in the upper quartile (≥11 295 mg/m\textsuperscript{2}).</td>
</tr>
<tr>
<td>Armuand 2017\textsuperscript{a}</td>
<td>Swedish National Patient Register (n=552)</td>
<td>Patients born between 1973-1977</td>
<td>0-21 years</td>
<td>Age matched controls from the general population</td>
<td>Not reported</td>
<td>HR 0.79 before 1988 HR 0.71 after 1988 0.90</td>
<td>Malignancy of the eye, CNS or leukemia</td>
</tr>
</tbody>
</table>

\textsuperscript{a}CCSS=Childhood Cancer Survivor Study, Gy=Gray, RR=Relative risk, CI=Confidence interval, BCSS=British Childhood Cancer Survivor Study, O/E=Observed/Expected, RT=Radiation therapy, AIEOP=Italian Pediatric Hematology and Oncology Association, CNS=Central nervous system, HR=hazard ratio.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study cohort</th>
<th>Offspring (no.), (CS no.)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Cancer (treatment)</th>
<th>Health risk outcomes measures</th>
<th>Risk estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chariello 2000</td>
<td>Female CCS - Ontario Cancer Registry, diagnosis &lt; 20 yr (1964–1988)</td>
<td>594 singleton pregnancies (340 survivors)</td>
<td>Questionnaire</td>
<td>Internal comparison: Patients treated with non-sterilizing surgery only or no treatment</td>
<td>Medical records. 5 treatment groups: non-sterilizing surgery; AA; AP irradiation: low ≤ 25 Gy, high &gt; 25 Gy; AA plus AP irradiation; and all other treatments</td>
<td>Congenital malformations (22 cases)</td>
<td>CS with AP irradiation: OR 0.45 (0.12–1.70)</td>
</tr>
<tr>
<td>Winter 2003</td>
<td>CCS - Danish Cancer Registry, diagnosis &lt;20 yr (1943–1996)</td>
<td>2130 offspring (born to 550 female and 550 male survivors)</td>
<td>Registry linkage</td>
<td>General Danish Population</td>
<td>Registry-based information on radiotherapy (yes/no)</td>
<td>Sex ratio alterations (2130 offspring)</td>
<td>-male (0.99): female (1.00) ratio vs Danish population (1.06)</td>
</tr>
<tr>
<td>Winter 2004</td>
<td>CCS - Danish Cancer Registry, diagnosis &lt; 20 yr (1943–1996)</td>
<td>2630 offspring (4676 female and male survivors)</td>
<td>Registry linkage</td>
<td>Offspring of siblings</td>
<td>Registry-based information on RT (yes/no)</td>
<td></td>
<td>-no effect of RT on the M:F ratio -p for trend with ovarian dose = 0.51</td>
</tr>
<tr>
<td>Reuljen 2007</td>
<td>BCSS - National Registry of Childhood Tumours, diagnosis &lt; 15</td>
<td>6232 offspring (born to 3218 female and male survivors)</td>
<td>Questionnaire obtained from general practitioners</td>
<td>General population of England and Wales</td>
<td>Registry-based information on RT (yes/no) and CT (yes/no).</td>
<td>Sex ratio alterations (6232 offspring)</td>
<td>-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)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age</td>
<td>Study Design</td>
<td>Outcomes</td>
<td>Odds Ratio (95% CI)</td>
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<tr>
<td>Magelsen 2008</td>
<td>Norway</td>
<td>1940-1991</td>
<td>First-born offspring (number not stated)</td>
<td>Hospital-based information on cancer treatment</td>
<td>OR 1.00 (0.77-1.30)</td>
<td></td>
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<tr>
<td>Winter 2009</td>
<td>Denmark</td>
<td>&lt;20 yr (1950-1996)</td>
<td>Offspring of siblings</td>
<td>Congenital malformations (7 cases)</td>
<td>OR 0.7 (0.4-1.6) in female CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mueller 2009</td>
<td>USA</td>
<td>&lt;20 yr (1973-2000)</td>
<td>Comparison subjects selected from birth records</td>
<td>Congenital malformations (10 cases)</td>
<td>Sex ratio alterations (1898 offspring)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mad</td>
<td>Finland</td>
<td>&gt;26331 offspring</td>
<td>Registry-based information on RT</td>
<td>Cancer (65 cases in</td>
<td>-Offspring of CS: SIR 1.67 (1.29-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table above provides a summary of studies examining congenital malformations and radiation exposure. The studies included in the table vary in their design and outcomes, with some focusing on hospital-based information and others on registry-based data. The odds ratios and confidence intervals (CI) for different outcomes are also provided.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methodology</th>
<th>Linkage</th>
<th>Linkage Details</th>
<th>Comparison</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wint at-Harju 2010</td>
<td>Cancer Registry, diagnosis &lt;35 yr (1953–2004) of 12735 survivor parents of 9877 children born after their parent’s diagnosis (4764 female and 5113 male CS)</td>
<td>Linkage</td>
<td>- Indirect comparison with offspring of siblings</td>
<td>(yes/no)</td>
<td>children born after their parent’s diagnosis</td>
<td></td>
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<tr>
<td>Green 2010</td>
<td>National Wilms Tumor LTFUS: Female CCS (and partners of male CS of Wilms tumor) (&lt;Jan 2007)</td>
<td>Linkage</td>
<td>Self-administered questionnaires</td>
<td>Internal comparison</td>
<td>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</td>
<td>Congenital malformations (44 cases)</td>
</tr>
<tr>
<td>Winters 2010</td>
<td>CCS – Danish Cancer Registry, diagnosis &lt;20 yr (1990–1996)</td>
<td>Linkage</td>
<td>Registry linkage</td>
<td>Offspring of siblings</td>
<td>Registry-based information on RT (yes/no)</td>
<td>Untoward disorders measured as hospitalization in childhood assuming that hospitalization is an indicator of multifactorial genetic disease (1053 discharge diagnoses in CS’ offspring)</td>
</tr>
<tr>
<td>Wint</td>
<td>CS – Danish 472 CS; 145 case</td>
<td>Registry</td>
<td>- Internal comparison: Medical records, including</td>
<td>Genetic diseases</td>
<td>Dose–response findings:</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Source</td>
<td>Diagnosis</td>
<td>Radiation Exposure</td>
<td>Linkage</td>
<td>Outcome</td>
<td>Radiation Dose Categories</td>
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<tr>
<td>Signorelli 2012</td>
<td>CCSS - Canada/USA, diagnosis &lt;21 yr (1970–1986)</td>
<td>4699 offspring (born to 1627 female and 1128 male CS)</td>
<td>Self-administered questionnaire</td>
<td>Internal comparison</td>
<td>Medical records, including AAD score: 1-3 (lowest, middle and top tertile exposure) and individual pre-conception RT doses to the gonads</td>
<td>Congenital anomalies defined as cytogenetic abnormalities, single-gene defects, and congenital malformations (129 offspring with congenital anomalies)</td>
</tr>
</tbody>
</table>

- 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 pre-conception 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) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Country</th>
<th>Age Range</th>
<th>First Pregnancies</th>
<th>Exposure</th>
<th>Controls</th>
<th>Outcomes</th>
<th>RR</th>
<th>M:F Ratio</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haggard 2014</td>
<td>15-39 yr (1982-2007)</td>
<td>Western Australia Cancer Registry</td>
<td>1894 female CS</td>
<td>5 treatment groups; surgery only, CT only, RT only, CT and RT, and all other types and therapy combinations</td>
<td>1894 completed pregnancies</td>
<td>Population-based comparisons without cancer</td>
<td>Congenital malformations (12 cases)</td>
<td>RR 0.78 (0.41-1.37)</td>
<td>M:F Ratio: RR 1.05 (0.98-1.10)</td>
<td>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)</td>
</tr>
<tr>
<td>Seppälänen 2016</td>
<td>&lt;35 yr (1953-2004)</td>
<td>Finnish Cancer Registry</td>
<td>3929 CS; 2197 female and 1732 male CS</td>
<td>2202 offsprings; 4450 offsprings of young adult CS</td>
<td>Registry-based information on RT (yes/no)</td>
<td>Congenital malformations (220 cases)</td>
<td>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)</td>
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</tr>
</tbody>
</table>

CCS = Childhood Cancer Survivors, yr = years, AA = alkylating agents, CT = chemotherapy, Gy = gray, M:F = male:female, CCR = Childhood Cancer Registry, CS = Cancer Survivors, SIR = standardized incidence rates, RT = radiotherapy, P = prevalence ratio. 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

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 lab:
• Consideration of oocyte cryopreservation

Preconception Assessment
Factors that may influence Maternal Health
e.g. Compromised cardiac function
• Anthracyclines/monoclonal agent exposure
• Chest irradiation
• Hypertension
• Wilms tumour treated with abdominal irradiation
• Gestational Diabetes
• Abdominal irradiation

Factors that may influence Fetal Health
• Maternal Cranial irradiation
• Spontaneous pregnancy loss
• Abdominal/pelvic irradiation causing uterine dysfunction
• Miscarriage/premature delivery/Low Birth Weight

POI = premature ovarian insufficiency; AFC = antral follicle count; AMH = anti-Mullerian hormone.
References


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22. United Kingdom Children’s Cancer Study Group Late Effects Group: Therapy based long term follow up practice statement Aohwcou:
Assessment of the postpubertal survivor

Endocrine and fertility assessment
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- Preconception assessment

POI
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- Fertility
  - Cryopreserved ovarian tissue or oocytes
  - Donor oocytes

Not POI
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Wishes conception now?
- Attempt natural conception
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  - Fertility later:
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- e.g. Compromised cardiac function
  - Anthracycline/molecular agent exposure
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    - e.g. Hypertension
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