fortune Journals

Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654

Age At Cancer Diagnosis and Its Impact on Fertility After Systemic Oncological Treatment in Childhood, Adolescent and Young Adult (Caya) Cancer Survivors – A Systematic Review

Charlotte Deltour[1,‡], Justine Himpe[2,3,‡], Fleur Bonny[4], Charlotte Smet[4], Lore Lapeire[2,3,5,†], Chloë De Roo[1,5,*,†]

Abstract

Background: A cancer diagnosis presents unique challenges across different life stages, particularly concerning the impact of oncologic treatments on fertility in children, adolescents, and young adults. This review investigates how age at cancer diagnosis affects fertility outcomes after systemic cancer treatment.

Methods: A systematic review was performed based on relevant literature obtained from 4 databases up until July 1st, 2024.

Results: For women, a younger age at diagnosis generally leads to better fertility outcomes post-treatment, such as preserved ovarian function and successful pregnancies. In contrast, an older age at diagnosis is associated with diminished ovarian reserve, reduced fertility potential, and a higher risk of premature ovarian insufficiency. In men, the results are mixed. Some studies suggest that younger age at diagnosis predicts better spermatogenesis recovery post-chemotherapy, but conflicting evidence questions the protective effect of prepubertal testes against cytotoxic damage.

Conclusion: Understanding how age at cancer diagnosis influences fertility is essential for making informed decisions about fertility preservation. The impact of age on fertility outcomes is more significant in females than males. Future research should aim to clarify the mechanisms behind age-related differences in fertility outcomes and develop personalized fertility preservation strategies for cancer survivors of all ages.

Keywords: Oncofertility; Gonadotoxicity; Reproductive health; Chemotherapy; Adolescents and young adults; AYA; Childhood cancer survivors; Age at diagnosis

Introduction

Over the past 40 years, the treatment of children, adolescents and young adults with cancer has become increasingly successful [1,2]. In several European and North American countries, the five-year overall survival for children with cancer (aged 0-14 years old) has increased from nearly 30% in the 1960s to more than 80% [3-5]. The most common tumor types for children are brain and central nervous system (CNS) tumors, leukemias, and lymphomas [3-5]. Cancer in adolescents and young adults (AYAs) is defined by the National Cancer Institute and by the working group of the European Society for Medical Oncology

Affiliation:

[1]Department of Reproductive Medicine, Ghent University Hospital, 9000 Ghent, Belgium

[2]Department of Medical Oncology, Ghent University Hospital, 9000 Ghent, Belgium

[3]Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, 9000 Ghent, Belgium

[4]Faculty of Medicine and Health Sciences, Ghent University, 9000 Ghent, Belgium

[5]AYA Research Centre and Hub (ARCH), Ghent University, 9000 Ghent, Belgium

[‡]These authors contributed equally to this work.

[†]These authors contributed equally to this work.

***Corresponding author:**
Dr. Chloë De Roo, Department of Reproductive Medicine, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium.

Citation: Charlotte Deltour, Justine Himpe, Fleur Bonny, Charlotte Smet, Lore Lapeire, Chloë De Roo. Age At Cancer Diagnosis and Its Impact on Fertility After Systemic Oncological Treatment in Childhood, Adolescent and Young Adult (Caya) Cancer Survivors – A Systematic Review. Archives of Internal Medicine Research. 7 (2024): 297-320.

Received: October 02, 2024
Accepted: October 16, 2024
Published: November 28, 2024

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

(ESMO) and the European Society for Paediatric Oncology (SIOPE) as diagnoses occurring among those aged between 15 and 39 years [6,7]. The most common malignancies in AYAs (>90% of cases) are leukaemia, lymphoma, sarcoma, melanoma, breast cancer, testicular cancer, colorectal cancer, thyroid cancer and brain tumours [6]. In AYAs, survival gains are more modest than in children, and for some tumor types, survival is worse in AYAs than in children with the same disease [6,8]. For all cancers in AYAs combined, survival improved over time from 79% in 1999–2002 to 82% in 2005–2007 [8].

The period of childhood and adolescence is characterized by rapid physiological, personal, and psychological growth. Therefore, a cancer diagnosis can have a significant impact on well-being on several levels, such as the development self-identity, peer relationships, autonomy and sexuality [6,9]. Despite improving overall survival rates, certain treatments, such as chemotherapy and/or pelvic irradiation, can temporarily or permanently adversely affect fertility [1]. This is considered one of the pivotal late effects of childhood cancer treatment. Infertility rates for male childhood cancer survivors (CCS) range from 42% to 66%, while for female CCS, they range from 11% to 26%. Many childhood and AYA cancer survivors are not aware of their reproductive capacity, which can result in unexpected problems later on due to impaired fertility or infertility [10]. Despite extensive research on the impact of cancer treatment on fertility, the reproductive impact of cancer treatment is still not completely understood, taking into account the patient's age at the time of cancer treatment.

Modern cancer treatments are often multimodal treatments consisting of a combination of radiotherapy, surgery and systemic treatment. Systemic cancer therapy is continually advancing, with standard treatments now incorporating not only classical cytotoxic chemotherapy but also targeted therapy and immunotherapy. The effects of chemotherapeutic agents on fertility are well-documented in the literature, showing varying degrees of gonadotoxicity that depend on factors such as the mechanism of action, dosage and duration of treatment, and the patient's age at the time of therapy [11-13]. However, the impact of targeted therapy and immunotherapy on fertility remains less understood. Recently, we described the various mechanisms by which systemic oncologic therapy can affect fertility in a comprehensive review [14].

In the context of fertility, it is important to understand that the regulation of reproduction is intricately governed by the hypothalamic-pituitary-gonadal (HPG) axis, a complex system with inhibitory and excitatory factors involving three glands and their attendant hormones. The HPG axis orchestrates the synthesis of sex steroids and promotes gametogenesis through the release of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The axis undergoes three major activations: embryonic stage, postnatal mini-puberty, and puberty [15].

During embryonic development, primordial germ cells migrate to the gonadal ridge, where they differentiate into either ovarian or testicular cells. In females, oogonia proliferate rapidly to form primary oocytes, which, if surrounded by granulosa cells, become primordial follicles. The number of follicles decreases over time due to various factors, leading to complete depletion at menopause. Meanwhile, the hypothalamic GnRH pulse generator becomes functional, influencing gonadotrophin secretion [16]. In male, the gonocytes enter in arrest in the G0 phase and stay mitotically inactive until after birth. During mini-puberty, observed in the initial 6 months in boys and 2-4 years in girls, elevated levels of gonadotrophins and sex hormones are noted. In boys, Leydig cells produce testosterone influenced by LH, reaching maximum levels at 2-3 months and diminishing at 6 months, while FSH peaks at 11-15 days. In girls, LH reaches maximum values in the first month and FSH after 2-3 months. Mini-puberty is crucial for male fertility, yet its significance in females is understudied [17,18].

After years of quiescence, the third activation occurs at puberty, characterized by the achievement of fertility and changes in body features [15]. The reduced hormonal levels increase once again during pubertal transition [16]. In the testis, FSH leads to the proliferation of Sertoli cells in the seminiferous tubuli. Sertoli cells have many functions and are important conductors for spermatogenesis [18]. LH and FSH have complementary functions in follicle development and ovulation [19]. In the ovaries, LH ensures the secretion of estradiol through the secretion of androgens and the transfer to granulosa cells. In these granulosa cells, ovarian follicles are stimulated by FSH. Although the follicles are stimulated by FSH, it is LH that takes care of the final follicle maturation. Hence, a deficiency in the production of these hormones reduces female fertility [19].

Oogenesis, the process of egg formation, involves mitosis and meiosis, with primordial germ cells differentiating into oogonia and subsequently forming primordial follicles [16]. Meiosis in women passes over an extended period of time [20]. By the time puberty is about to begin, the oocytes are still in prophase I of meiosis [16]. Oocyte maturation involves completing meiotic divisions, with a narrow fertilization window of 12 to 14 hours following ovulation [20,21]. Follicles serve as the functional units of the ovaries, where the oocyte matures, surrounded by granulosa and theca cells [22]. At birth, the ovaries contain approximately 1 to 2 million oocytes comprising the ovarian reserve, of which only about 300 will mature during a woman's reproductive life [16].

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

The ovarian reserve serves as a critical determinant of a woman's fertility potential, impacting both spontaneous conception and pregnancy outcomes achieved through assisted reproduction techniques. The term "diminished ovarian reserve" (DOR) is often used in fertility research and is mainly correlated to low anti-Müllerian hormone (AMH) levels, but different definitions are used in the literature [23,24]. Some authors also use measurements of FSH and antral follicle count (AFC) [23]. Some studies compare AMH values with those of healthy control subjects, while others calculate age-specific cutoff values because AMH values gradually decrease with age [25,26]. Other markers for evaluation of ovarian function include the incidence of amenorrhea and estradiol levels.

Spermatogenesis, a continuous process, produces mature spermatozoa in the testes and takes approximately 42-76 days. The process includes spermatocytogenesis, meiosis, and spermiogenesis, culminating in the release of spermatozoa managed by Sertoli cells [27]. Semen analysis is pivotal in assessing male fertility, providing insights into testicular functionality, duct system permeability, and accessory gland secretory activity [28]. According to the World Health Organization (WHO) guidelines, semen analysis involves macroscopic and microscopic evaluations of volume, color, pH, viscosity, round cells, liquefaction time, sperm count, motility, concentration, and morphology. However, it is recognized that regular semen analysis might not precisely identify fertility impairment etiology or predict reproductive success [29].

This systematic review focuses on the fertility of female and male survivors of childhood and AYA cancer and specifically on how age at the time of diagnosis and systemic cancer treatment can affect fertility in different ways.

Materials and Methods

Literature search

This review is registered in the International prospective register of systematic reviews (PROSPERO; registry under number CRD42024503999). This systematic review comprises a literature search in 4 databases, including PubMed, Embase, Google Scholar and Web of Science. The search terms used were ‘child’, ’adolescent’, ‘young adult’, ‘AYA’, ’fertility’, ‘infertility’, ‘childhood cancer survivor’, ‘chemotherapy’, ’cancer’, ‘cancer treatment’, ‘cancer survivor’, ‘reproductive health’, ‘drug effects’ and ‘age of onset’. The last search update was on 1 July 2024. Filters were applied for English language and study type (to exclude reviews, posters, editorials and case reports). In cases of overlapping or duplicated data from the same researchers, the most recent or complete study was selected for inclusion. Articles from decades ago with lasting relevance up to now are exceptionally included.

Selection criteria and outcomes of interest

The population of interest consists of humans who had survived cancer and underwent systemic cancer treatment during their childhood, adolescence or young adulthood. Since information on immunotherapy and targeted therapy is scarce, this review focuses on cytotoxic chemotherapy. All studies reporting on impact of age at diagnosis were considered for inclusion. A multistage screening process was used to identify relevant articles. Two investigators (CS and FB) established the inclusion and exclusion criteria. The retrieved studies were initially screened for potential eligibility based on the title, abstract, and content by CS, FB and CD. Disagreements about study eligibility were resolved by discussion with the remaining authors.

The major exclusion criteria were as follows: focusing solely on fertility preservation, adverse pregnancy outcomes, psychological concerns, radiotherapy treatment, animal studies. Furthermore, studies that did not stratify participants by age at diagnosis were excluded.

The article search is illustrated in the PRISMA flowchart (Figure 1).

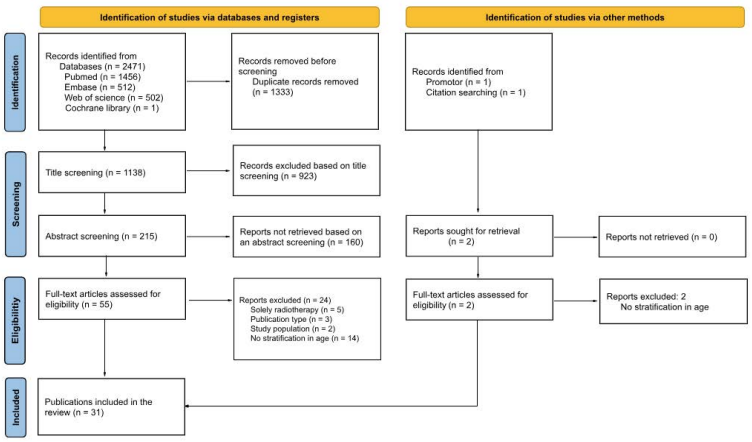

Figure 1: PRISMA 2020 flow diagram for systematic reviews

Citation: Charlotte Deltour, Justine Himpe, Fleur Bonny, Charlotte Smet, Lore Lapeire, Chloë De Roo. Age At Cancer Diagnosis and Its Impact on Fertility After Systemic Oncological Treatment in Childhood, Adolescent and Young Adult (Caya) Cancer Survivors – A Systematic Review. Archives of Internal Medicine Research. 7 (2024): 297-320.

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Results

Women

Table 1 shows a list of the included studies regarding female childhood, adolescent and young adult survivors. The results of these studies are summarized in table 2.

Author	Year of publication	Country of origin	Research design	Aim of the study	Treatment period
Elchuri [26]	2016	USA	Cross-sectional study	Evaluation of AMH levels and DOR in female childhood cancer survivors and to assess treatment related factors.	Unreported
Charpentier [30]	2014	Canada	Cross-sectional study	Evaluation of AMH level in childhood cancer survivors and too asses treatment and patient related factors.	Unreported
George [31]	2019	USA	Cross-sectional study	Evaluation of the utility of AMH for the assessment of DOR in adolescent and young adult (AYA)-aged survivors of childhood cancer.	Unreported
Van den Berg [32]	2021	The Netherlands, Ireland, France, Germany, Denmark, Norway, UK, Italy, Czech Republic, Israël	Case-control study	Evaluation of treatment related risk factors for fertility impairment in long-term female childhood, adolescent and young adulthood (CAYA) cancer survivors, with a focus on chemotherapy and radiotherapy.	1963-2011
Behringer [33]	2013	Germany	Cross-sectional study	Evaluation of gonadal functions in survivors of Hodgkin lymphoma.	Unreported
Behringer [34]	2005	Germany	Cross-sectional study	Evaluation of the menstrual status after Hodgkin lymphoma therapy.	1994-1998
Irene Su [35]	2020	USA	Prospective cohort study	Evaluation of the trajectory of ovarian function over two decades following cancer treatment and assess the influence of treatment gonadotoxicity and age.	Unreported
Silva [36]	2019	Portugal	Prospective cohort study	A prospective evaluation of ovarian reserve markers in young women with breast cancer exposed to chemotherapy, to research the influence of patient and treatment-related factors.	2014-2016
Lie Fong [37]	2009	The Netherlands	Cross-sectional study	To evaluate treatment related gonadal toxicity by assessing AMH in a cohort of adult female childhood cancer survivors (CCS).	1958-2000
Chamani [38]	2024	USA	Retrospective cohort study	To evaluate pre- and posttreatment AMH levels in a cohort of breast cancer patients receiving dose-dense chemotherapy	2015-2019
Chiarelli [39]	1999	Canada	Retrospective cohort study	A comparison of the infertility risk between female childhood cancer survivors who received abdominal-pelvic radiation, chemotherapy with alkylating agents and who were treated by nonsterilizing surgery only.	1964-1988
Van Der Kaaij [40]	2012	European countries (incl. France, the Netherlands, Belgium, Italy, …)	Retrospective cohort study	To evaluate the impact of treatment regimens on POF and motherhood in Hodgkin's lymphoma survivors, with special focus on nonalkylating chemotherapy, dose-response relationships for alkylating chemotherapy and the influence of age at treatment.	1964-2004
De Bruin [41]	2008	The Netherlands	Retrospective cohort study	To evaluate treatment effects on risk of premature menopause in 5-year Hodgkin lymphoma (HL) survivor.	1965-1995
Sklar [42]	2006	USA	Retrospective cohort study	To evaluate the incidence of premature menopause in participants in the multicenter Childhood Cancer Survivor Study (CCSS) and to identify risk factors.	1970- 1986

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Felicetti [43]	2020	Italy	Retrospective cohort study	To assess the prevalence of gonadal dysfunction and to determine risk factors in hematologic malignancy survivors.	1990-2012
Krawczuk-Rybak [44]	2019	Poland	Cross-sectional study	To evaluate the hormonal markers of gonadal function in adolescent leukemia survivors, treated in childhood with different levels of aggressiveness.	Unreported
Park [45]	2024	Korea	Retrospective cohort study	To examine the effects of gonadotoxic cancer treatment on treatment-related amenorrhea in CAYA patients	2011-2022
Beneventi [46]	2015	Italy	Case-control study	To compare uterine and ovarian volumes and uterine artery (UA) Doppler bloodflow among women who were treated for childhood cancer regimens versus healthy controls.	Unreported
Barton [47]	2013	USA	Retrospective cohort study	To evaluate infertility and time to pregnancy in the multicenter Childhood Cancer Survivor Study (CCSS).	1992-2004
Melin [48]	2017	Finland	Retrospective cohort study	To compare the use of fertility treatments in early onset (0-34 years) cancer survivors giving birth to siblings and to identify the subgroups that are more likely to require fertility treatments.	1993-2004

Diminished ovarian reserve

Two cross-sectional studies showed that higher age at diagnosis was significantly associated with lower AMH after childhood cancer treatment [26,30]. The first study by Elchuri et al. included 49 pediatric cancer survivors who were 10-21 years old at the time of the study. DOR was defined as an AMH level below the fifth percentile for age-matched controls. Ninety percent of the subjects were pubertal, and 69% had attained spontaneous menarche by the appropriate age of under 15 years. Among those who had reached menarche, 20% still demonstrated DOR. Additionally, older age at diagnosis was identified as a significant predictor of low AMH following treatment [26]. The second study by Charpentier et al. included 66 adult female survivors to evaluate the AMH serum level after treatment with chemotherapy. The AMH levels were measured by an enzyme immunoassay with a range of 1 to 150 pM and a sensitivity of 1 pM. AMH level was considered low if <14.30 pM. The median age at cancer diagnosis was 11.9 years old. Multivariate analysis showed that older age at diagnosis was significantly associated with lower AMH after treatment. They reported a decrease of 3.3 pM for each additional year of age at diagnosis [30].

Some studies evaluated the influence of age at diagnosis by treatment regimen or risk group for gonadotoxicity. A retrospective study of 190 female cancer survivors evaluated the influence of age at treatment on AMH levels within different treatment groups with respectively low, moderate or high risk of gonadotoxicity. Low AMH means below the assay's age-specific reference range and FSH levels were categorized as normal (≤12 mIU/mL), intermediate (>12 mIU/mL and <40 mIU/mL), or menopausal (≥40 mIU/mL). Within the low gonadotoxic risk group, survivors diagnosed with cancer after 11 years of age were 5.4 times more likely to have low AMH compared with those diagnosed before 11 years. In this low-risk group, there was a higher proportion of patients with low AMH and normal FSH in the group diagnosed after the age of 11 years compared to those diagnosed before 11 years. This association with age at diagnosis was not observed in the other high-risk groups [31]. In a case-control substudy of the PanCareLIFE project, fertility impairment was assessed using both questionnaire data and hormonal data (FSH and AMH). Cases were defined as women with impaired fertility if they met at least one of eight predefined criteria: primary amenorrhea with or without information on AMH levels, secondary amenorrhea with or without information on AMH levels, a high FSH level along with a low AMH level (while under 40 years of age at the time of the study), a low AMH level (while under 30 years of age at the time of the study), use of artificial reproductive techniques before the age of 40 years, ever tried to conceive for at least 1 year without success before the age of 40 years. All survivors received treatment between 1963 and 2011 at ages ranging from 0 to 24 years. Since age at diagnosis was a factor in matching controls to cases, the researchers could only assess the impact of age at diagnosis on the strength of the associations between fertility impairment and treatment factors. Therefore, the effects of the chemotherapy and radiotherapy treatments were modeled separately for three diagnostic age groups (0–<6 years, ≥6–<12 years and ≥12 years). A total of 450 cases (survivors with fertility impairment) and 882 matched controls (survivors without fertility impairment) were included. Treatment with busulfan, lower abdominal radiotherapy, and total body irradiation appeared to impair fertility regardless of the age at diagnosis. In contrast, treatment with melphalan and procarbazine seemed to negatively affect fertility primarily in

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

survivors diagnosed at a younger age (younger than 6 years). These data should be interpreted with caution because certain age groups for specific chemotherapeutic agents or radiation at specific body sites had very few participants due to the heterogeneity of the included patients [32]. A Dutch cohort study compared 185 adult female survivors of childhood cancer with 42 control subjects. The median follow-up time was 18.1 years and the median age at the time of treatment was 5.8 years. AMH concentrations did not differ significantly in survivors compared with controls, nor with treatment before or after menarche. They did find that the type of treatment (such as total body irradiation, abdominal radiotherapy and chemotherapy with three or more procarbazine cycles) was a predictor of residual ovarian function after treatment. Another finding was that women with undetectable AMH levels (< 0.1µg/L) were significantly older at diagnosis compared with the remaining group of survivors. But this should be interpreted with caution since more women in this group had undergone whole-body or abdominal radiation [37].

The literature described above related mainly to cancers in childhood and adolescence. The following studies evaluated fertility parameters in young adults and focused mainly on patients with Hodgkin lymphoma and breast cancer. An analysis from the German Hodgkin Lymphoma Study Group HD13 to HD15 trials, which focused on early- and advanced-stage Hodgkin lymphoma (HL), evaluated fertility parameters in women under 40 years old at diagnosis who were in ongoing remission for at least one year post-therapy. The mean age at fertility assessment was 32 years, with a mean observation period of 46 months since treatment ended. Results were categorized by age groups (18 to 29 years and 30 to 45 years). Women under 30 years old with early-stage HL, treated with two to four cycles of doxorubicin, vinblastine, dacarbazine, and bleomycin (ABVD), exhibited normal mean AMH levels (> 2 µg/L). However, AMH levels were reduced in survivors aged 30 years and older. Following 6 to 8 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), mean AMH levels were 0 µg/L in both age groups, with the highest FSH levels seen in women over 30 years. After treatment for advanced-stage HL, 82% of women under 30 years had regular menstrual cycles, compared to only 45% of women in the older age group. The time to resume menstrual activity was significantly longer in advanced-stage patients and was strongly related to age [33]. Another study by the same author reported that the incidence of amenorrhea post-HL therapy was higher in women over 30 years old at the time of treatment [34].

Only two prospective studies were found on the influence of age at diagnosis and fertility outcomes, both conducted in AYAs. In the first cohort study, AMH levels were measured in survivors aged 18-39 years at variable time points since completion of cancer treatment, every 6 months for up to 18 months. They evaluated the AMH trajectory over time for different age groups and different gonadotoxic risk groups. This study included 763 participants, mean age at enrollment 33.3 years and mean age at cancer diagnosis 25.9 years. The most common cancers were breast cancer (26.9%), lymphoma (24.8%) and thyroid cancer (18.0%). After low or moderate gonadotoxic treatments, AMH levels increased over 2-3 years, plateaued for 10-15 years, and then began to decline. In contrast, following highly gonadotoxic treatments, AMH levels were consistently lower, peaking at 2-3 years before declining shortly thereafter. Younger age at treatment was associated with higher AMH trajectories, but this protective effect was not observed in survivors exposed to highly gonadotoxic treatments. Given that the mean AMH trajectory varied by both the gonadotoxicity risk of the cancer treatment and age at diagnosis, an overall interaction between age and gonadotoxicity was tested and found to be significant. In the low gonadotoxicity group, AMH trajectories were similar across age groups, with some separation over time between those older than 30 and the younger groups. For the moderate gonadotoxicity group, a greater difference was observed between those older than 30 years and those younger than 25 or between 25 to 30 years. In the high gonadotoxicity group, AMH trajectories were similar for the 25 to 30 years and older than 30 years groups, but differed from those of the youngest age group [35]. Another prospective observational study included premenopausal women with breast cancer, aged 18-40 years at diagnosis, who were candidates for (neo)adjuvant chemotherapy. Patients were evaluated before, during, and at least nine months after the end of chemotherapy. Age at recruitment was negatively correlated with AMH levels at the final follow-up. However, no significant correlation was found between patients' age and final AFC. Additionally, age at recruitment was significantly lower in patients who recovered ovarian function compared with those who did not [36]. In a retrospective study conducted from 2015 to 2019, the impact of adjuvant dose-dense chemotherapy regimens on ovarian reserve was investigated, focusing on pre- and post-treatment AMH levels in women with breast cancer. This study included patients receiving dose-dense chemotherapy with doxorubicin and cyclophosphamide, with or without paclitaxel. The median age at treatment start was 31 years (range 24-43), and the follow-up AMH timeframe was 1.5 years (median 18 months) after chemotherapy initiation. Patients under 35 years had a median pre-treatment AMH of 3.0 ng/mL and post-treatment AMH of 0.19 ng/mL, while patients aged 35 and above had a median pre-treatment AMH of 2.7 ng/mL and post-treatment AMH of 0.1 ng/mL. The investigation into the recovery of AMH levels showed that in the "Early AMH" group, with AMH measured up to 12 months post-treatment, the median age was 33 years. These patients had a median pre-treatment AMH level of 3.75 ng/mL, which dropped to 0.1 ng/mL post-treatment. In the "Late

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

AMH" group, where AMH was measured after 12 months post-treatment, the median age was 31 years. The median pre-treatment AMH level for this group was 2.7 ng/mL, and it decreased to 0.2 ng/mL post-treatment. Overall, the findings indicate a significant and sustained decrease in AMH levels following chemotherapy, signifying a marked decline in ovarian reserve regardless of the patients' age [38].

Premature ovarian insufficiency

Premature ovarian insufficiency (POI) is defined as the loss of normal ovarian function before a woman reaches age 40. High FSH levels are usually the gold standard for identifying patients with POI. Clinically, it refers to patients with irreversible amenorrhea lasting longer than 12 months. Other terms used are premature menopause or premature ovarian failure [39–41].

The following three studies found that age at initial treatment is a risk factor for POI. An old retrospective comparative study included 830 female patients with a cancer diagnosis between 1964-1988 before the age of 20 years and evaluated menopausal status using questionnaires. Women diagnosed after puberty had a significantly increased risk of menopause when treated with abdominal-pelvic radiation plus alkylating agents compared with the surgery group. This risk was non-significantly increased in pre-pubertal patients, but a direct comparison between age groups was not made [39]. A cohort study of 518 female HL survivors, aged 14 to 40 years at treatment, showed that age at first treatment was an independent risk factor for early menopause. Chemotherapy-adjusted hazard ratios for early menopause were 2.6 for patients aged 22 to 28 years and 5.2 for patients aged 29 to 39 years compared with ages 14 to 21 years at first treatment. The cumulative risk of menopause at age 40 did not differ much by age at diagnosis, but the time to early menopause was much longer in women treated at an early age [41]. Another study of 460 HL patients, treated between 15 and 40 years of age, showed that the cumulative risk of POI differed depending on age at treatment. However, this result was mainly determined by the patients who were directly menopausal during treatment. A total of 94 women experienced acute menopause during first-line treatment: 0%, 15%, 44%, and 41% for those aged 15 to 24, 25 to 34, 35 to 44, and 45 years or older, respectively. If menstruation resumed post-treatment, the cumulative risk of POI was independent of the age at treatment. The overall cumulative risk of POI was 17% for women treated before the age of 25 and 32% for those treated at age 35 or older. Overall, there was a 23% increase in the risk of POI per year of age at treatment starting from age 15. The impact of age on the occurrence of POI was smaller in women treated with alkylating chemotherapy compared to those treated without it [40].

Four studies did not identify age at diagnosis as a risk factor for premature menopause or POI. The first study by Sklar et al. assessed the incidence of and risk factors for premature menopause in 2819 survivors of the multicenter Childhood Cancer Survivor Study (CCSS). Median age at cancer diagnosis was 7 years (range = 0-20) and median age at study was 29 years (range = 18-50). They found that the risk of nonsurgical premature menopause was related to attained age, but found no association with age at diagnosis after adjustment for attained age [42]. The second study is an Italian cohort study with 131 female survivors of pediatric hematologic malignancies who evaluated fertility parameters in the long-term follow-up clinic. The patients were all younger than 18 years at diagnosis and at least 5 years had elapsed since the end of cancer treatment. In this study, age at diagnosis did not appear to be a risk factor for POI [43]. The third study is a cross-sectional study of 69 acute lymphoblastic leukemia survivors including 25 females with a median age at diagnosis of 9 years old. The authors concluded that females treated before and during puberty presented comparable levels of FSH, LH, E2, and inhibin B [44]. The fourth study was a retrospective cohort study conducted at SNUH from 2010 to 2022, which included female patients diagnosed with cancer before 21 years of age. The median age at cancer diagnosis was 15 years (range: 2–20), with a median age at last visit of 20 years (range: 5–35). Of the patients, 76.9% had reached menarche at diagnosis. Menstruation resumed in 70.6% of patients after one year. Age at diagnosis did not significantly affect treatment-related amenorrhea outcomes [45].

Uterine volume

A case-control study involving 127 women who underwent treatment for childhood cancer with bone marrow transplantation (BMT), chemotherapy, and total body irradiation (TBI), and 64 age-matched healthy controls, compared uterine and ovarian volumes as well as Doppler blood flow from the uterine artery. The median age at treatment was 10 years, with a median follow-up time of 9 years. All conditioning treatments were linked to smaller uterine volumes compared to controls. Women treated with chemotherapy alone had larger uterine volumes (24.3% reduction) than those who received BMT with or without additional chemotherapy or radiotherapy (71.1% reduction). Patients treated before the age of 5 had smaller uteri compared to those treated between ages 5 and 10 or older than 10 years. Additionally, there was a positive correlation between age at treatment and uterine volume [46].

Fertility treatment and pregnancy

Another way to look at fertility parameters is to evaluate pregnancy rate or the need for artificial reproductive techniques. In an analysis of The Childhood Cancer Survivor Study (CCSS), clinical infertility was defined by patients who tried unsuccessfully to conceive at any time for 1 year or longer. Total infertility included clinically infertile women and women who reported ovarian failure, which was defined

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

as never having had a period or having stopped menstruating for at least 5 years or longer. Compared to their siblings, cancer survivors exhibited a higher risk of clinical and total infertility, though no significant association was found with the age at primary diagnosis [47]. A Finnish study analyzed 1974 post-diagnosis deliveries among cancer survivors and 6107 deliveries among their female siblings between 2004 and 2013. The study assessed the risk associated with various fertility treatments, including IVF/ICSI (in vitro fertilization/ intracytoplasmic sperm injection), intrauterine insemination, and ovulation induction. Survivors diagnosed as adults (aged 25–34 years) had the highest odds of utilizing fertility treatments (7.7%) compared to their siblings aged 25 years or older (3.2%) when giving birth. Conversely, cancer survivors diagnosed in childhood had the lowest overall odds of using fertility treatments (3.7%) compared to their siblings but had significantly increased odds of undergoing intrauterine insemination [48].

Table 2: Overview of the results for women.

Author	Number of participants	Diagnosis	Age at diagnosis	Age at the time of the study/ last visit	Treatment	Outcomes	Conclusion
Elchuri [26]	49	Leukemia (n = 21); Lymphoma (n = 5); Renal tumors (n = 13); Sarcoma (n = 10)	Mean age 6.4 years (±4.8)	Mean age 14.9 years (±3.3)	Alkylating ChT (91.8%); Heavy metals (26.5%); unilateral/bilateral ovarian RT (resp.6.1%/12.2%); BMT (12.2%)	AMH and FSH	Being diagnosed with cancer in later childhood or during the teenage years was significantly associated with an increased likelihood of having DOR compared to being diagnosed in early childhood
Charpentier [30]	66	Leukemia (n = 31); Hodgkin lymphoma (n = 29); Sarcoma (n = 6)	Median age 11.9 years (range 1.8–17.3)	Median age 23.3 years (range 18.2–34.2)	Surgery (9.1%); RT (56.1%); ChT (100%)	AMH	In univariate and multivariate analysis older age at diagnosis was associated with lower AMH. There was a decrease of 3.3 pM for each additional year of age at diagnosis.
George [31]	190	Leukemia (n = 72); HL (n = 24); NHL (n = 11); Osteosarcoma (n = 19); Other sarcoma (n = 23); Wilms tumor (n = 13); Other (n = 12)	Mean age 8 years (±5.0)	Mean age 16.7 years (±2.3)	Alkylating ChT (67,9%); HSCT (16.3%); unilateral oophorectomy (2.1%); ovarian RT (24.2%); cranial RT ≥ 30 Gy (3.2%)	AMH and FSH	Among the future infertility risk groups, a significant difference in the odds of low AMH by age at diagnosis was observed only in those with a low future infertility risk.

Van den Berg [32]	450	Leukemia (n = 137); Lymphomas (n = 81); CNS tumours (n = 52); Neuroblastoma and peripheral nervous cell tumours (n = 49); Renal tumours (n = 41); Bone and soft tissue tumours (n = 50); Germ cell tumours (n = 28); Other (n = 12)	Median age 9.5 years (range 0-24)	Median age 30.0 years	SCT (34.2%); Surgery (6.2%); ChTy +/- surgery (42.4%); RT +/- surgery (4.1%); ChT and RT +/- surgery (42.5%)	Hormonal measurements (FSH and AMH) data from questionnaires (including primary or secondary amenorrhea, use of assisted reproductive technologies, and unfulfilled desire to conceive)	Treatment with melphalan and procarbazine seemed to adversely affect the fertility of survivors treated at younger ages, whereas treatment with busulfan, lower abdominal RT, and TBI appeared to impair fertility regardless of the age at diagnosis.
Behringer [33]	562	HL	Mean age 28 years (range 18-49)	Mean age 32 years (range 20-45)	Alkylating containing ChT BEACOPP (41%); Non-alkylating ChT ABVD (58%)	Questionnaire data (Menopause Rating Scale, pregnancies, menstrual status,…); Hormonal data (FSH, LH, estradiol, AMH)	Women under 30 years exhibited normal mean AMH levels (> 2 µg/L) after two to four cycles of ABVD for early-stage treatment, whereas survivors aged 30 years and older had compromised AMH levels. Following six to eight cycles of BEACOPP, mean AMH levels were 0 µg/L in both age groups, with the highest FSH levels observed in women over 30 years.
Behringer [34]	405	HL	15-29 years (60.5%) and 30-40 years (39.5%)	Not specified (median observation time after treatment 3.2 years (range 7 months to 6.3 years)	RT alone (7.9%); Combined-modality and ChT alone (92.1%)	A survey to evaluate the menstrual status	Amenorrhea occurred significantly more often in women older than 30 years of age at treatment.

Irene Su [35]	763	Leukemia (n = 63); Bone tumour/ sarcoma (n = 50); Breast (n = 205); Gynecologic (n = 72); Gastro-intestinal (n = 23); Lymphoma (n = 189); Skin (n = 24); Thyroid (n = 137)	Mean age 25.9 years	Mean age 33.3 years	Surgery (68%); RT (44.4%); ChT (67.4%); biologic therapy (4.3%); BMT or SCT (4.1%); ET (17%)	AMH trajectories over time	AMH trajectories were lower the higher the treatment age, and the protective effects of younger age declined in the late twenties when exposed to treatments with high gonadotoxicity
Silva [36]	38	Breast cancer	Mean age 32.9 years (range 25-39)	Last visit a mean of 2 years (range 1–3 years) after recruitment	ChT only (21%); ChT + ET (42%); ChT + TT (13%); CT + TT + ET (24%)	Self-reported menstrual data, AMH and FSH, AFC by vaginal ultrasound	Age at recruitment was negatively correlated with AMH levels at the final follow-up. Conversely, there was no significant correlation between patients' age and final AFC. Patients who recovered ovarian function were significantly younger at recruitment compared to those who did not recover. However, within the subgroups of women with or without POI and those reporting regular menses or not, age at recruitment did not show a significant difference.
Lie Fong [37]	182	ALL and NHL (n = 77); AML (n = 8); HL (n = 15); Neuroblastoma (n = 17); Sarcoma (n = 25); Wilms tumour (n = 28); Other (n = 12)	Median age 5.8 years (range 0.1–16.8)	Median age 25.5 year (range 17.0–47.4 year)	RT only (2%); non-alkylating ChT (38%); alkylating ChT (55%); ChT + abdominal or total body irradiation (8%)	AMH	AMH concentrations were not significantly different in survivors compared with controls, nor when treated before or after menarche. Women with undetectable AMH levels (< 0.1µg/L) were significantly older at diagnosis but more often they received abdominal RT or TBI.

Chamani [38]	57	Breast cancer	Median age 31 years (range 24-43)	unreported	Dose-dense chemotherapy with doxorubicin hydrochloride and cyclophosphamide, with or without paclitaxel (Taxol)	AMH	AMH concentration pre and posttherapy were not significantly different in relation to age at diagnosis
Chiarelli [39]	719	Lymphoma (n = 201); epithelial neoplasm (n = 129); CNS tumour (n = 93); leukemia (n = 79); soft tissue sarcoma (n = 50); bone tumour (n = 46); renal tumour (n = 46); gonadal and germ cell tumour (n = 29); other (n = 36)	Median age unknown (range 0-19)	Median age 28 (range 18-49)	Surgery (22,5%); alkylating ChT (20,8%); abdomino-pelvic RT (21,4%); alkylating ChT and abdomino-pelvic RT (9,8%); other (25,3%)	Menopausal status using questionnaires	Women diagnosed after puberty had a significantly increased risk of menopause when treated with abdominal-pelvic radiation plus alkylating agents compared with the surgery group. This risk was non-significantly increased in pre-pubertal patients.
Van Der Kaaij [40]	460	HL	Median age 30 years (range 15-40)	Median age 49 (range 25-76)	Non-alkylating ChT (32,8%); alkylating ChT (43,9%); RT above diaphragm (69,3%); RT below diaphragm (23,9%)	Menopausal status using questionnaires	The cumulative risk of POI is higher in older patients. However, this result was mainly determined by the patients who were directly menopausal during treatment. The impact of age on the occurrence of POI was less pronounced in women treated with alkylating chemotherapy compared to non-alkylating chemotherapy.
De Bruin [41]	518	HL	Median age 25 years (range 14-40)	Unreported, median follow up of 9.4 years	RT (36.1%); ChT (10%); RT + ChT (53,9%)	Data on menopausal status obtained from medical records	Age at first treatment was an independent risk factor for early menopause and the time to early menopause is longer in women treated at an early age.

Sklar [42]	2819	Leukemia (n = 1025); HL (n = 404); bone tumours (n = 324); renal tumours (n = 297); sarcomas (n = 271); neuroblastoma (n = 207); NHL (n = 154); brain tumours (n = 137)	Median age 7 years (range 0-20)	Median age 29 years (range = 18 – 50)	Surgery (10%); ChT (10%); RT (<1%); ChT + RT (17%); surgery + ChT (20%); surgery + RT (8%); surgery + ChT + RT (33%); SCT (1%)	Menopausal status using questionnaires	They did not identify age at diagnosis as a risk factor for POI.
Felicetti [43]	131	ALL (n = 65); HL (n = 33); NHL (n = 8); AML and MDS (n = 25)	Median age unknown (all patients younger then 18 years)	Median age 24.7 (range 21.5-28.3)	Abdominopelvic RT (21%); TBI (15%); cranial RT (5%); alkylating ChT (93%); non-alkylating ChT (7%) HSCT (40%)	FSH, LH, estradiol, AMH	They did not identify age at diagnosis as a risk factor for POI
Krawczuk-Rybak [44]	25	Acute lymphoblastic leukemia	Mean age 9.01 years (±4.27)	Mean age 18.74 years (±4.78)	Treatment according to BFM protocol—ALLIC 2002 (Acute Lymphoblastic Leukemia-Intercontinental) including cyclophosphamide	LH, FSH, inhibin B, AMH, estradiol	Females treated before and during puberty presented comparable hormone values.
Park [45]	143	Bone sarcoma (n = 23), ALL n = 21), NHL (n = 20), HL (n = 11), AML (, = 16), ovarian cancer (n = 17), brain tumor (n = 11), soft tissue sarcoma (n = 9), Ewing sarcoma (n = 5), others (n = 10)	Median age 15 years (2–20)	Median age 20 years (5–35)	ChT (74.1%), ChT + RT (25.9%). HSCT (25.9%)	LH, FSH, AMH, oestradiol, amenorrhoea	Age at diagnosis did not affect treatment related amenorrhea
Beneventi [46]	127	Nonmalignant hematologic disease (n = 31); hematologic malignancy (n = 63); lymphoma (n = 23): solid tumors (n = 10)	Median age 10 years (range 6–13)	Median age 19 years (range 13–30)	BMT (58%); ChT + BMT (15%); ChT + RT + BMT (5%); ChT + RT (5%); ChT (17%)	Uterine and ovarian volume, detection of follicles, and uterine artery pulsatility index by ultrasonography	Age at treatment correlated positively with uterine volume.
Barton [47]	3531	Leukemia (n = 1006); HL and NHL (n = 927); CNS tumour (n = 323); solid tumour (n = 1275)	Median age unknown (all patients younger then 21 years)	Median age 27.6 years (range 23.5-32.3)	Abdominal RT (24%); brain RT (26%); pelvic RT (17%); TBI (1%); BMT (2%); alkylating ChT (37%)	Infertility using questionnaire	Compared with their siblings, cancer survivors had an increased risk of clinical and total infertility but there was no significant association with age at primary diagnosis.

Citation: Charlotte Deltour, Justine Himpe, Fleur Bonny, Charlotte Smet, Lore Lapeire, Chloë De Roo. Age At Cancer Diagnosis and Its Impact on Fertility After Systemic Oncological Treatment in Childhood, Adolescent and Young Adult (Caya) Cancer Survivors – A Systematic Review. Archives of Internal Medicine Research. 7 (2024): 297-320.

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Melin [48]	1281	Leukemia (n = 156); Lymphoma (n = 246); CNS tumours (n = 119); epithelial neoplasms (n = 525); other (n = 235)	Median age unknown (range 0-34 years)	Unreported	ChT (33%); RT (32%); Surgery (39%)	Data on assisted reproductive technology and data on mothers giving birth	Survivors diagnosed as adults (aged 25–34 years) had the highest odds for use of fertility treatments (7.7%) compared to siblings aged 25 years or older (3.2%).

***Abbreviations:** ChT (chemotherapy), BMT (bone marrow transplantation), RT (radiotherapy), HSCT (hematopoietic stem cell transplantation), SCT (stem cell transplantation), ET (endocrine therapy), TT (targeted therapy), TBI (total body irradiation), ALL (acute lymphoblastic leukemia), HL (Hodgkin lymphoma), NHL (non-Hodgkin lymphoma), AML (acute myeloid leukemia), MDS (myelodysplastic syndrome), CNS (central nervous system)

Men

Table 3 shows a list of the included studies regarding male childhood, adolescent and young adult survivors. The results of these studies are summarized in table 4.

Table 3: Overview of the included studies for men.

Author	Year of publication	Country of origin	Research design	Aim of the study	Treatment period
Rautonen [49]	1992	Finland	Case-series	To assess the toxic effects of individual agents in survivors of childhood cancer.	1960-1985
Kenney [50]	2001	USA	Case-series	To evaluate the testicular reproductive adverse outcomes of high dose cyclophosphamide during childhood.	1960-1992
Thomson [51]	2001	UK	Case-control study	To evaluate testicular function in childhood cancer survivors.	Unreported
van Casteren [52]	2009	The Netherlands	Case-control study	To evaluate the gonadal toxicity of childhood cancer treatment using fertility markers, including inhibin B, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone.	Unreported
Tromp [53]	2011	The Netherlands	Cohort study	To evaluate long-term gonadal effects of cancer treatments, to identify treatment-related risk factors for hypergonadotropic hypogonadism, and to assess the association between FSH levels and the need for assisted reproductive techniques (ART) in adult male survivors of childhood cancer.	1966-2003
Romerius [54]	2011	Sweden	Cohort study	To evaluate disease- and treatment-related risk factors of azoospermia in childhood cancer survivors.	1970-2002
Rendtorff [55]	2012	Germany	Retrospective observational study	To assess the diagnostic value of hormones as markers of spermatogenesis in male childhood cancer survivors.	Since 1980
Behringer [33]	2013	Germany	Cross-sectional study	Evaluation of gonadal functions in survivors of Hodgkin lymphoma.	Unreported

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Haavisto [56]	2024	Sweden	Cross-sectional study	Long-term reproductive health and testosterone replacement therapy (TRT) needs in male survivors of childhood cancer.	1981- 2017
Namekawa [57]	2016	Japan	Retrospective data	To identify predictors of spermatogenesis recovery in testicular cancer patients after chemotherapy and to determine the recovery period for spermatogenesis.	1982-2001
Duca [58]	2019	Italy	Cohort study	To identify risk factors related to diagnosis, therapy, and age at treatment for adverse reproductive outcomes following childhood cancer treatment.	Unreported
Beaud [59]	2019	Canada	Retrospective pilot study	To compare reproductive outcomes and sperm damage between adult survivors of childhood leukemia and lymphoma, subdivided into those diagnosed before or after puberty, and men with no history of cancer.	Unreported
Krawczuk-Rybak [44]	2019	Poland	Cross-sectional study	To evaluate the hormonal markers of gonadal function in adolescent leukemia survivors, treated in childhood with different levels of aggressiveness.	Unreported
Felicetti [43]	2020	Italy	Retrospective cohort study	To assess the prevalence of gonadal dysfunction and to determine risk factors in hematologic malignancy survivors.	1990-2012

Hormonal testicular function

Hormone analysis is commonly employed in the majority of studies to evaluate gonadal function following childhood cancer treatment (Table 4). Reproductive parameters frequently examined include testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin B [43,53,55]. Deviation of hormone serum levels from clinical standards may indicate impaired testicular hormonal function. Typically, abnormal values are defined as follows: FSH > 10 U/l, LH > 15 U/l, testosterone < 11.0 nmol/l, inhibin B < 80pg/ml [53,55]. However, Beaud et al. used > 8 U/l as the cutoff for FSH levels, and Felicetti et al. utilized inhibin B values lower than 100 pg/mL as a cutoff [43,59]. Most studies differentiate in pubertal status, assessed by age in combination with using the Tanner staging method [51,58].

Three studies suggest a correlation between age at diagnosis and hormonal deficiencies [33,53,55]. The first study conducted by Tromp et al. focused in a cohort study in 2011 on 488 male cancer survivors with a median age at diagnosis of 7.8 years, lymphoma being the most common diagnosis. About 90% of the population received chemotherapy, primarily with alkylating agents, vinca-alkaloids, or antimetabolites. The results indicated that a higher age at diagnosis and a longer follow-up duration may be associated with an increased risk of elevated FSH levels [53]. Similar results were found in the retrospective observational study of Rendtorff et al. including 73 participants (median age of 10 years at diagnosis) where participants with pathological FSH values were significantly older than those with normal FSH levels (11.4 years, SD 5.6 versus 14.9 years, SD 6.6; p = 0.03). No significant difference in age was seen for inhibin B levels [55]. Also, the third study, a case series of Behringer et al. in 2013, the German Hodgkin Study Group HD13 to HD15 trials, showed more favorable hormone levels for younger survivors in all three trials when focusing on inhibin B and FSH. Regarding testosterone levels, survivors from HD14 and HD15 treatment also showed a significant age effect, with higher levels in younger men [33]. In contrast with these three studies were the data from the cohort study of Felicetti et al. in 2020, including 196 male CCS. A preservation of

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

sex hormone production was observed when anticancer treatments were performed at an older age (>10 years) [43].

Four studies found no correlation between age at diagnosis and hormonal levels. The first study, a case-control study of van Casteren et al. in 2009, studying 221 male cancer survivors and 74 normospermic controls, found no correlation between the age at which cyclophosphamide and procarbazine were administered and inhibin B levels, regardless of a low or high total cumulative dose of cyclophosphamide. These results suggest that a young age at the time of childhood cancer treatment does not provide a protective effect on gonadal function [52]. In the second study, Duca et al. included 102 patients, with a mean age at diagnosis of 6.2 years and a mean age at enrollment of 23.2 years. In terms of endocrine function and sperm concentration, there were no significant differences between the two age groups (<10 and ≥10 years old) [58]. The third study, a pilot study of Beaud et al. in 2019, stratified the CCS group (n = 13) by the age at diagnosis before (ages 4–14, n = 6) and after puberty (ages 15–17, n = 7). Analysis of mean serum testosterone and FSH levels revealed no significant differences between controls (12 age-matched healthy men) and CCS, regardless of age at diagnosis relative to puberty onset. However, some CCS (n = 4) exhibited elevated FSH levels indicative of non-obstructive azoo/oligozoospermia, irrespective of age at diagnosis [59]. In the last study of Krawczuk-Rybak et al., 69 AYA leukemia survivors (25 females and 44 males) were included. Males completed treatment before an average of 8.97 (± 4.38) years. There was no observed effect of the time of treatment (before vs. during puberty) on hormone levels, except for higher luteinizing hormone values in survivors treated before puberty compared to those treated during puberty [44].

A study conducted in Sweden, assessed long-term reproductive health and testosterone replacement therapy (TRT) needs in male survivors of childhood cancer, focusing on those aged 19-40 years. The 1212 participants were diagnosed between 1981 and 2017, with a median age at diagnosis of 7 years (range 0-17). At the time of the study, the median age was 29 years (range 19-40), with a median time of 21 years post-diagnosis (range 1-37). Self-reported data included the need for induced puberty, ongoing TRT, and having biological children. The study found that half of the survivors who required hormone therapy to induce puberty did not need ongoing TRT in young adulthood and had a good prognosis for partnering and fathering biological children. The other half required continued TRT, indicating long-term Leydig cell failure. Younger age at diagnosis was identified as a significant risk factor for long-term TRT needs (OR 0.90, 95% CI: 0.82–0.99, p = 0.027). An interesting observation was that men who had spontaneous pubertal development also initiated TRT during early adulthood, suggesting a decline in Leydig cell function over time [56].

Semen analysis and spermatozoal DNA integrity

In the previously described research like that of Rendtorff et al., 31% of the spermiograms were found abnormal, indicating oligozoospermia or azoospermia. In conclusion, nearly one-third of the participants experienced fertility impairment. There was a negative correlation between age at diagnosis and sperm concentration, suggesting a smaller risk of fertility impairment if boys were treated earlier in life, before puberty [55]. Also, Namekawa et al. identified younger at diagnosis (<25 years) as a significant clinical predictors of spermatogenesis recovery in testicular CCS after chemotherapy. Despite age at diagnosis being an independent predictor of normalization, there was no difference in the time to recover normospermia by age, which was seen at a median time of 40 months. The age gap between groups likely reflects age-related testicular degeneration rather than the ability to recover from chemotherapy-induced damage [57]. Contrasting results were seen in the case-series of Kenney et al. in 2001. They investigated sperm quality in male childhood sarcoma survivors, previously treated with high dose cyclophosphamide chemotherapy regimens. Of the 17 males undergoing semen analysis, patients treated before puberty exclusively displayed abnormal semen analyses suggesting exposure before puberty did not provide protection [50].

Also, five studies found no correlation between age at diagnosis/treatment and semen analysis [43,49,51,54,59]. In a study of Rautonen et al. in 1992, 55 males were diagnosed and treated for childhood malignancies between 1960 and 1985 at a single institution, 51% were found to be azoospermic. Factors such as age at diagnosis, testicular irradiation, and specific therapeutic agents were associated with the risk of azoospermia. However, in multivariate analysis, these findings were not statistically significant. While the vulnerability of the prepubertal testis to spermatotoxicity is speculated to be less than the pubertal testis, this study does not support that speculation, particularly with the use of cyclophosphamide [49].

In the second study, Thomson et al. studied 33 men with a median age of 21.9 years (range 16.5 – 35.2) who were diagnosed with cancer at a median age of 10.0 years (2.2 – 16.9). Among the ten azoospermic patients, seven were prepubertal at diagnosis, challenging the notion that the prepubertal testis is protected from cytotoxic insult. However, no significant correlation was found between age at diagnosis or time since treatment and sperm concentration in non-azoospermic CCS [51]. Also, the study of Romerius et al. found similar proportion of subjects with azoospermia for all CCS diagnosed at ≤10 years or the age group above 10 years [54]. These studies were in line with the results of Beaud et al. and Felicetti et al. analysing azoo/oligozoospermia, sperm chromatin and DNA integrity. Age at cancer diagnosis did not emerge as a risk factor for spermatogenesis damage [42,49].

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Testicular volume

Only the study of Duca et al. specifically reported about the impact of age on testicular volume. The study indicates a trend towards slightly lower total testicular volume in patients treated during pubertal age. However, this difference becomes nonsignificant when adjusted for age at diagnosis and treatment, suggesting that age alone may not be a determining factor in testicular volume outcomes [58].

Table 4: Overview of results for men.

Author	Number of participants	Diagnosis	Age at diagnosis	Age at the time of the study/ last follow-up visit	Treatment	Outcomes	Conclusion
Rautonen [49]	55	Leukaemia (n = 2), lymphoma (n = 12), Wilms' tumor (n = 9), neuroblastoma (n = 7), different sarcomas (n = 13), and other (n = 3)	Median age 10 years (range 1 day to 15 years)	Median age 20 years (range 18-43)	Different combinations of surgery, RT, and ChT	Semen quality	Neither age at diagnosis nor the interactions between age and the receipt of vincristine, cyclophosphamide, nor testicular RT, had an independent effect on the risk of azoospermia.
Kenney [50]	17	Sarcoma	Median age 12 years (range 4 –19)	Median age 25 years (range 16 –34)	Alkylating ChT	Semen quality	58.8% had azoospermia and 29.4% had oligospermia, seen exclusively in those treated before puberty.
Thomson [51]	33	ALL (n = 15), HL (n = 6), Ewing's sarcoma (n = 5), NHL (n = 2), other (n = 6)	Median age of 10 years (range 2.2–16.9)	Median age of 22 years (range 16.5-35.2)	ChT and RT	Semen quality	Of the ten azoospermic patients, seven were prepubertal at diagnosis, providing cogent evidence that the prepubertal testis is not afforded protection from cytotoxic insult. No significant correlation between age at diagnosis or time since treatment and sperm concentration in non-azoospermic survivors.
van Casteren [52]	221	ALL, AML, HL, NHL, malignant mesenchymal tumor	Median age 5 years (range 0 – 15)	Median age 23 years (range 18 –41)	ChT and RT	Inhibin B	There was no correlation between the age of cyclophosphamide and procarbazine treatment and inhibin B levels. There was no gonadal protective effect of young age at the time of cyclophosphamide administration, whether they received low or high total cumulative dosage of cyclophosphamide.
Tromp [53]	488	Leukaemia, lymphoma, kidney tumor, Brain/ CNS tumors, bone tumor, soft tissue sarcoma, neuroblastoma	Median age 7.8 years (range 0.0 –17.8)	Median age 21.0 years (range: 18.0 –46.0 years)	ChT and/or surgery and/or RT	FSH	Higher age at diagnosis and longer follow-up are associated with increased risk of elevated FSH levels.

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Romerius [54]	129	Leukaemias (n = 21), brain tumors (n = 27), HL (n = 19), NHL (n = 9), testicular cancer (n = 9, Wilms' tumor (nephroblastoma) (n = 11) and others (n = 33)	Median age 10 (range 0.10–17)	Median age 29 years (range 20–46)	brain surgery (n=16), surgery only (except brain surgery) (n=16), ChT only (in some cases combined with surgery) (n=35), RT to the testes (n=1), non-testicular RT (in some cases combined with surgery) (n=13), both ChT and RT (in some cases combined with surgery) (n=48)	Semen quality	Similar proportion of subjects with azoospermia for all CCS diagnostic subgroups diagnosed at ≤10 years and the entire CCS group. When analyzed by treatment, both ChT-only and combined ChT and RT groups had the highest proportion of azoospermia, CCS diagnosed at ≤ 10 years of age showed similar results.
Rendtorff [55]	73	ALL (n =27), HL (n =11), NHL (n =6), AML (n =3), CML (n =3), brain tumors (n =8), soft-tissue sarcoma (n =5), renal tumors (n =4), osteosarcoma (n =3), extracranial germ-cell tumors	Mean age 10 years (range 1–18)	Mean age 25 years (range 19–43)	not specified	FSH, Semen quality	Pathological FSH values associated with older age at diagnosis. Participants with normospermia were younger at diagnosis than those with oligozoospermia or azoospermia, suggesting a negative correlation between age at diagnosis and sperm concentration.
Behringer [33]	761	HL	Mean age 34 years (range 18-49)	Mean age 38 years (range 19-57)	ChT	Inhibin B, FSH, and testosterone	Younger survivors had more favorable hormone levels (inhibin B, FSH, and testosterone).
Haavisto [56]	1212	ALL (n = 330), AML (n = 47), Lymphoma (n = 198), sarcoma (n = 130), neuroblastoma (n = 39), CNS tumors (267), others (n = 201)	Median age 7 years (range 0-17)	Median age 29 years (range 19-40)	ChT (73.5%), surgery (33.9%), Abdominopelvic RT (1.7%), cranial RT (11.6%), HSCT (8.2%)	Need for induced puberty, ongoing TRT, and having biological children	Younger age at diagnosis was a significant risk factor for long-term TRT needs.
Namekawa [57]	35	Testicular cancer	Not specified (range 17-41)	Not specified, observation period was 13.3 years (± 5.6)	High orchiectomy and cisplatin based ChT	Semen quality	Age at diagnosis < 25 years associated with better post-ChT semen recovery. No difference in time to recover normospermia by age.
Duca [58]	102	ALL (n = 67), NHL (n= 11), HL (n = 8), Wilms tumor (n = 5), AML (n =4), and hepatoblastoma (n= 3)	Mean age 6.2 years (± 4.2)	Mean age 23.2 (± 5.4 years)	ChT only, ChT plus RT, HSCT	Testicular volume (using ultrasound)	Patients treated at age 10 years or older had slightly but significantly lower total testicular volume compared to those treated before age 10.
Beaud [59]	13	ALL, HL and NHL	Mean age 12.8 years (± 1.3)	Mean age 27.8 years (± 1.6)	Vinca alkaloids, alkylating agents, anthracyclines	Semen quality, and serum hormone analysis consisting of LH, FSH, testosterone	No significant differences in testosterone and FSH levels between controls and CCS. Four males with impaired fertility regardless of the age at diagnosis.

Citation: Charlotte Deltour, Justine Himpe, Fleur Bonny, Charlotte Smet, Lore Lapeire, Chloë De Roo. Age At Cancer Diagnosis and Its Impact on Fertility After Systemic Oncological Treatment in Childhood, Adolescent and Young Adult (Caya) Cancer Survivors – A Systematic Review. Archives of Internal Medicine Research. 7 (2024): 297-320.

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

Krawczuk-Rybak [44]	44	ALL	Mean age 8.97 years (±4.38)	Mean age 17.23 years (±3.24)	not specified		No observed effect of the time of treatment on hormone levels, except for higher LH values in survivors treated before puberty.
Felicetti [43]	196	ALL (n = 89), HL (n = 55) and NHL (n = 32), AML and MDS (n = 20)	< 18 years	Median age 24.6 (range 21.8-29.4)	Abdominopelvic RT (16%), cranial RT (6.5%), ChT (100%) of which mostly alkylating agents (95%)	Semen quality, and serum hormone analysis consisting of LH, FSH, testosterone	Preservation of sex hormone production observed when anticancer treatments performed at an older age (>10 years). Age at cancer diagnosis did not emerge as a risk factor for spermatogenesis damage.

***Abbreviations:** ChT (chemotherapy), BMT (bone marrow transplantation), RT (radiotherapy), HSCT (hematopoietic stem cell transplantation), SCT (stem cell transplantation), ET (endocrine therapy), TT (targeted therapy), TBI (total body irradiation), ALL (acute lymphoblastic leukemia), HL (Hodgkin lymphoma), NHL (non-Hodgkin lymphoma), AML (acute myeloid leukemia), MDS (myelodysplastic syndrome), CNS (central nervous system), CML (chronic myeloid leukemia)

Discussion

This systematic review explored the impact of age at cancer diagnosis on fertility parameters following systemic cancer treatment in both women and men. In general, younger individuals exhibit better fertility outcomes compared to older patients.

For female cancer survivors, we summarize that advancing age at diagnosis is generally associated with a higher risk of diminished ovarian reserve, compromised hormone levels, premature ovarian insufficiency (POI) and increased risk of infertility in comparison to women who have not had an oncologic treatment. This trend holds across various cancer types and treatment regimens. However, some studies suggest that age at diagnosis may not always significantly impact fertility, indicating variability based on specific treatments, individual health conditions, and the ovarian reserve at baseline. Specifically, the gonadotoxic risk of a regimen is crucial for predicting future fertility risk, with a less pronounced protection of young age in highly gonadotoxic regimens. Older age at diagnosis predicts lower AMH levels post-treatment, which is crucial for determining ovarian reserve and fertility potential. However, this protective effect of age on AMH levels is less evident in regimens with high gonadotoxic risk. Correspondingly, the influence of age on the incidence of POI is less pronounced in female patients treated with highly gonadotoxic regimens, such as alkylating chemotherapy, compared to those treated with lower gonadotoxic regimens. This manuscript underscores the need to assess the baseline ovarian reserve and monitor these parameters throughout treatment and follow-up to evaluate fertility potential and inform family planning decisions.

As for men, some studies do suggest a correlation between age at diagnosis and hormonal deficiencies, however contrasting findings are observed in other studies. The discrepancy in findings regarding the influence of age at diagnosis on hormonal levels underscores the multifactorial nature of hormonal dysregulation post-cancer treatment. Factors such as treatment protocols, specific chemotherapeutic agents, and individual patient susceptibility may contribute to the observed variations. In addition to hormonal function, semen analysis serves as a direct indicator of male fertility potential post-cancer treatment. The studies reviewed here reveal heterogeneous findings regarding the impact of age at diagnosis on semen parameters. While some studies suggest a negative correlation between age at diagnosis and sperm concentration, others fail to establish a significant association. The study by Namekawa et al. highlights clinical predictors of spermatogenesis recovery post-chemotherapy, indicating that younger age at diagnosis is associated with better outcomes in terms of normalized semen parameters. However, Kenney et al. present contrasting findings, suggesting that exposure before puberty does not necessarily confer protection against sperm quality impairment. Moreover, studies by Rautonen et al. and Thomson et al. challenge the notion of prepubertal testis protection against cytotoxic insult, with significant proportions of azoospermic patients diagnosed during prepubertal stages. These findings emphasize the need for continued monitoring of semen parameters post-treatment, irrespective of age at diagnosis. The impact of age at cancer diagnosis on testicular volume is relatively underexplored, with limited studies addressing this aspect.

It should be noted that the comprehensive synthesis of evidence faces challenges due to the diversity of fertility assessment methods, such as questionnaires, hormonal markers, and ultrasound evaluations of reproductive organs. Additionally, the absence of standardized definitions and outcomes for fertility further complicates this process [60–62].

The influence of age at cancer diagnosis on fertility

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

outcomes post-treatment represents a complex interplay of biological, psychological, and sociocultural factors. Several biological mechanisms may underlie the observed age-dependent differences in fertility parameters following systemic cancer treatment. First, the age-related declines in ovarian reserve and testicular function may exacerbate the reproductive repercussions of cancer treatment in older patients [63–65]. Second, hormonal fluctuations associated with aging, such as declines in gonadotropin levels and alterations in sex steroid production, may further contribute to impaired fertility in older cancer survivors [64–68]. In addition to biological factors, psychosocial considerations play a pivotal role in shaping fertility outcomes among cancer survivors. Younger patients may experience heightened distress and anxiety regarding the potential loss of fertility and future reproductive options, underscoring the importance of early fertility preservation interventions and psychosocial support services. Conversely, older individuals may confront unique challenges related to family planning, including concerns regarding parental age at conception, financial stability, and caregiving responsibilities for children born after cancer treatment [69–72].

Although age at diagnosis is a crucial factor influencing fertility outcomes in cancer survivors, the choice of chemotherapeutic regimen also plays a pivotal role in shaping gonadotoxic risk. Especially alkylating agents, such as cyclophosphamide and busulfan, are known for their significant gonadotoxic effects [14].

Our study highlights the critical need for tailored fertility preservation strategies based on age at cancer diagnosis. Younger patients may benefit from proactive fertility preservation measures such as sperm, oocyte or ovarian tissue cryopreservation prior to initiating cancer treatment, whereas older patients may require comprehensive fertility counseling and advanced reproductive technologies to optimize their chances of conceiving post-treatment [11,12,73,74].

Integrating age-specific considerations into oncofertility practice underscores the importance of early and comprehensive fertility counseling for cancer patients. Cryopreservation emerges as a vital tool for preserving fertility in cases where gonads are directly affected, diminishing ovarian oocyte reserves and sperm production. However, for patients experiencing hypothalamic-pituitary axis dysfunction, cryopreservation may not offer a viable solution, as oocyte reserves and sperm production remain unaffected albeit unstimulated due to hormonal deficits. In such instances, the focus shifts to reactivating the hormonal axis through interventions like hormone replacement therapy. The question emerges whether cryopreservation, which may affect pubertal development, is the optimal approach in every case and at all times, especially considering age differences in our selected studies. By offering a spectrum of fertility preservation options tailored to individual circumstances, healthcare providers can empower survivors to make informed decisions that safeguard their reproductive health and overall well-being [11,12,73-75].

Additionally, healthcare providers should prioritize discussions surrounding fertility preservation options and family planning considerations with cancer patients at the time of diagnosis, irrespective of age, to empower informed decision-making. The integration of fertility preservation into comprehensive cancer care requires a multidisciplinary approach involving oncologists, reproductive endocrinologists, psychologists, and other healthcare professionals. Collaborative efforts are needed to develop evidence-based guidelines for fertility preservation in cancer patients across the lifespan, taking into account age-specific considerations, disease characteristics, and treatment modalities. We strongly recommend the incorporation of standardized fertility outcomes in upcoming clinical trials assessing both new and established treatments, aiming to evaluate their long-term effects on fertility. Future research endeavours should focus on elucidating the long-term reproductive outcomes stratified by age at diagnosis, thereby informing personalized survivorship care strategies and optimizing reproductive health outcomes for this vulnerable population.

Critical appraisal

Several limitations of this review warrant attention. First, the potential for selection bias and small sample sizes in many of the included studies could influence the generalizability of the results. Participants who responded to surveys or follow-ups may differ significantly from those who did not, potentially skewing the findings. Additionally, some studies excluded participants with incomplete records, which could bias the results towards those with more regular follow-ups. The exclusion of certain participant groups, such as those currently using hormonal contraception, might lead to an overestimation or underestimation of fertility impairment among cancer survivors.

Furthermore, many studies utilized retrospective designs, which inherently come with limitations such as selection bias, recall bias, and incomplete data. The retrospective nature also means that changes in treatment protocols over time could not be consistently accounted for, potentially impacting the relevance of the findings to current clinical practices. Treatment protocols in many included studies have evolved, meaning older studies might not accurately reflect outcomes associated with contemporary, sometimes less gonadotoxic, treatment regimens.

Additionally, the significant reliance on self-reported data for outcomes such as menopausal status, fertility history, and hormone levels introduces a risk of misclassification and

recall bias, potentially affecting the accuracy of the findings. Many studies also did not include appropriate control groups, such as healthy individuals or patients undergoing different treatment regimens, limiting the ability to draw strong causal inferences about the impact of cancer treatments on fertility and gonadal function.

The diversity in cancer diagnoses and significant variability in treatment regimens, including differences in chemotherapy protocols, radiation doses, and hormonal therapies, also present challenges. This heterogeneity makes it difficult to pool data and draw definitive conclusions about specific treatment effects. Several studies had short follow-up periods or provided only cross-sectional data, limiting the ability to assess long-term outcomes and the progression of gonadal function over time. Longitudinal studies with extended follow-up periods are needed to better understand the enduring effects of cancer treatment on fertility.

Moreover, as stated before, the studies varied in the markers used to assess reproductive health, such as AMH, inhibin B, and other hormonal levels, as well as semen analysis. The timing of these measurements, in relation to the menstrual cycle, treatment stages, or use of contraception, was not always consistent or reported, potentially affecting the reliability of these markers as indicators of ovarian or testicular function. Adding to the complexity, there are significant inconsistencies among the articles regarding the best methods for evaluating fertility. Some studies focus on hormonal levels, others on the quality of oocytes and sperm, the need for fertility treatments, or the ability to conceive and carry a pregnancy to term. This lack of consensus further complicates the interpretation of findings and the establishment of standardized assessment protocols.

The age at diagnosis versus puberty as a marker for assessing fertility risk also poses a challenge. Should the age be considered in terms of chronological age or based on physical developmental characteristics? This question remains unanswered and adds another layer of complexity to the evaluation of fertility outcomes. Finally, variations in the geographical location and demographics of study populations, including differences in healthcare systems and accessibility, might affect the applicability of the findings to different populations. Addressing these limitations is crucial for providing a comprehensive understanding of the current state of research while highlighting areas that require further investigation.

Conclusions

In conclusion, our study underscores the critical influence of age at cancer diagnosis on fertility outcomes in both male and female survivors. While younger patients generally exhibit better fertility prospects, advancing age at diagnosis in women is associated with diminished ovarian reserve and increased infertility risks. For men, the relationship between age at diagnosis and fertility parameters is less clear, necessitating further research. This conclusion is summarized in figure 2.

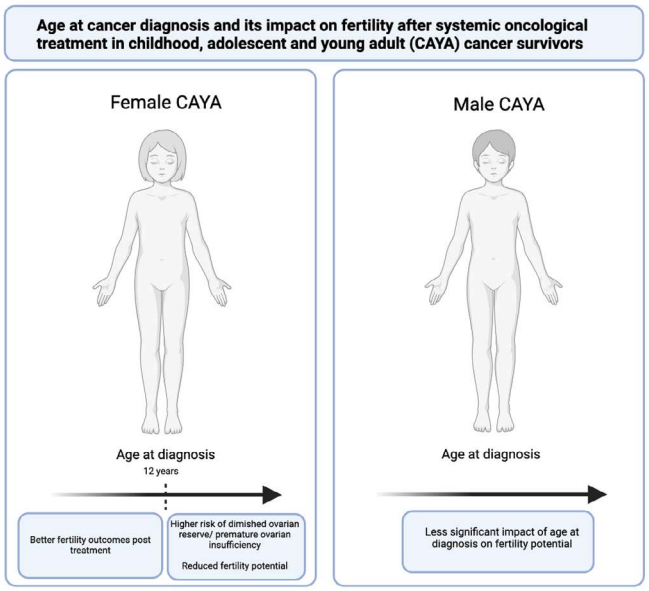

Figure 2: Age at cancer diagnosis and its impact on fertility after systemic oncological treatment in childhood, adolescent and young adult (CAYA) cancer survivors

Future directions should therefore focus on evaluating the appropriateness and timing of cryopreservation, ensuring it is neither too premature nor unnecessarily invasive, especially in the case of men. Long-term prospective follow-ups with yearly documentation focusing on reproductive health (by e.g. assessing AMH, pituitary gonadal axis, pubertal development and sperm analysis), reproductive outcomes (conception mode, time to pregnancy, obstetric outcomes, offspring), potential relapse (due to fertility preservation/restoration and pregnancy), are crucial for understanding the enduring effects of cancer treatment on fertility. Additionally, exploring the exact mechanisms by which chemotherapy affects gonadal tissues will provide a deeper understanding and aid in developing personalized treatment plans. Differentiating the impact of treatments based on chronological age versus developmental stage is another critical area for future research. Tailored fertility preservation strategies and comprehensive counseling are vital for optimizing reproductive health outcomes for cancer survivors.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Green, D. M.; Sklar, C. A.; Boice, J. D.; et al. Ovarian

Failure and Reproductive Outcomes after Childhood Cancer Treatment: Results from the Childhood Cancer Survivor Study. J Clin Oncol 27 (2009): 2374-2381.

2. Balcerek, M.; Reinmuth, S.; Hohmann, C.; et al. Suspected Infertility after Treatment for Leukemia and Solid Tumors in Childhood and Adolescence. Dtsch Arztebl Int 109 (2012): 126-131.

3. Ellison, L. F.; Xie, L.; Sung, L. Trends in Paediatric Cancer Survival in Canada, 1992 to 2017. Health Rep 32 (2021): 1-15.

4. Phillips, S. M.; Padgett, L. S.; Leisenring, W. M.; et al. Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity. Cancer Epidemiol Biomarkers Prev 24 (2015): 653-663.

5. Winther, J. F.; Kenborg, L.; Byrne, J.; et al. Childhood Cancer Survivor Cohorts in Europe. Acta Oncol 54 (2015), 655-668.

6. Ferrari, A.; Stark, D.; Peccatori, F. A.; et al. Adolescents and Young Adults (AYA) with Cancer: A Position Paper from the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE). ESMO Open 6 (2021).

7. Anderson, B.; Albritton, K. CLOSING THE GAP: RESEARCH AND CARE IMPERATIVES FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER CLOSING THE GAP: RESEARCH AND CARE IMPERATIVES FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER 2 0608020F Overview of the Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG) Priority Recommendations from the AYAO PRG Roundtable.

8. Trama, A.; Botta, L.; Foschi, R.; et al. Survival of European Adolescents and Young Adults Diagnosed with Cancer in 2000–07: Population-Based Data from EUROCARE-5. Lancet Oncol 17 (2016): 896-906.

9. Sodergren, S. C.; Husson, O.; Robinson, J.; et al. Systematic Review of the Health-Related Quality of Life Issues Facing Adolescents and Young Adults with Cancer. Quality of Life Research 26 (2017): 1659.

10. Lehmann, V.; Chemaitilly, W.; Lu, L.; et al. Gonadal Functioning and Perceptions of Infertility Risk Among Adult Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study. J Clin Oncol 37 (2019): 893-902.

11. Anderson, R. A.; Amant, F.; Braat, D.; et al. ESHRE Guideline: Female Fertility Preservation†. Hum Reprod Open (2020).

12. Oktay, K.; Harvey, B. E.; Partridge, A. H.; et al. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology 36 (2018): 1994-2001.

13. Lambertini, M.; Peccatori, F. A.; Demeestere, I.; et al. Fertility Preservation and Post-Treatment Pregnancies in Post-Pubertal Cancer Patients: ESMO Clinical Practice Guidelines†. Annals of Oncology 31 (2020), 1664-1678.

14. Himpe, J.; Lammerant, S.; Van den Bergh, L.; et al. The Impact of Systemic Oncological Treatments on the Fertility of Adolescents and Young Adults-A Systematic Review. Life (Basel) 13 (2023).

15. Abreu, A. P.; Kaiser, U. B. Pubertal Development and Regulation. Lancet Diabetes Endocrinol 4 (2016): 254.

16. Djahanbakhch, O.; Ezzati, M.; Zosmer, A. Reproductive Ageing in Women. J Pathol 211 (2007): 219–231.

17. Nordenström, A. Potential Impact of Mini-Puberty on Fertility. Ann Endocrinol (Paris) 83 (2022): 250–253.

18. Neto, F. T. L.; Bach, P. V.; Najari, B. B.; et al. Spermatogenesis in Humans and Its Affecting Factors. Semin Cell Dev Biol 59 (2016): 10-26.

19. Bosch, E.; Alviggi, C.; Lispi, M.; et al. Reduced FSH and LH Action: Implications for Medically Assisted Reproduction. Hum Reprod 36 (2021): 1469-1480.

20. Mehlmann, L. M. Stops and Starts in Mammalian Oocytes: Recent Advances in Understanding the Regulation of Meiotic Arrest and Oocyte Maturation. Reproduction 130 (6): 791-799.

21. Bianchi, S.; Macchiarelli, G.; Micara, G.; et al. A. Ultrastructural Markers of Quality Are Impaired in Human Metaphase II Aged Oocytes: A Comparison between Reproductive and in Vitro Aging. J Assist Reprod Genet 32 (2015): 1343.

22. Cosgrove, C. M.; Salani, R. Ovarian Effects of Radiation and Cytotoxic Chemotherapy Damage. Best Pract Res Clin Obstet Gynaecol 55 (2019), 37-48.

23. Santaballa, A.; Márquez-Vega, C.; Rodríguez-Lescure; et al. Multidisciplinary Consensus on the Criteria for Fertility Preservation in Cancer Patients. Clin Transl Oncol 24 (2022): 227–243.

24. Anderson, R. A.; Cameron, D.; Clatot, F.; et al. Anti-Müllerian Hormone as a Marker of Ovarian Reserve and Premature Ovarian Insufficiency in Children and Women with Cancer: A Systematic Review. Hum Reprod Update 28 (2022): 417–434.

25. Lunsford, A. J.; Whelan, K.; McCormick, K.; et al. Antimüllerian Hormone as a Measure of Reproductive Function in Female Childhood Cancer Survivors. Fertil Steril 101 (2014): 227–231.

26. Elchuri, S. V.; Patterson, B. C.; Brown, M.; et al. Low Anti-Müllerian Hormone in Pediatric Cancer Survivors in the Early Years after Gonadotoxic Therapy. J Pediatr Adolesc Gynecol 29 (2016): 393–399.

27. Holstein, A. F.; Schulze, W.; Davidoff, M. Understanding Spermatogenesis Is a Prerequisite for Treatment. Reprod Biol Endocrinol 1(2003).

28. Baskaran, S.; Finelli, R.; Agarwal, A.; et al. Diagnostic Value of Routine Semen Analysis in Clinical Andrology. Andrologia 53 (2021).

29. Barbăroșie, C.; Agarwal, A.; Henkel, R. Diagnostic Value of Advanced Semen Analysis in Evaluation of Male Infertility. Andrologia 53 (2021): e13625.

30. Charpentier, A. M.; Chong, A. L.; Gingras-Hill, G.; et al. Anti-Müllerian Hormone Screening to Assess Ovarian Reserve among Female Survivors of Childhood Cancer. Journal of Cancer Survivorship 8 (2014): 548–554.

31. George, S. A.; Williamson Lewis, R.; Schirmer, D. A.; et al. Early Detection of Ovarian Dysfunction by Anti-Mullerian Hormone in Adolescent and Young Adult-Aged Survivors of Childhood Cancer. J Adolesc Young Adult Oncol 8 (2019): 18–25.

32. Van Den Berg, M. H.; Van Dijk, M.; Byrne, J.; et al. Treatment-Related Fertility Impairment in Long-Term Female Childhood, Adolescent and Young Adult Cancer Survivors: Investigating Dose-Effect Relationships in a European Case-Control Study (PanCareLIFE). Human Reproduction 36 (2021): 1561-1573.

33. Behringer, K.; Mueller, H.; Goergen, H.; et al. Gonadal Function and Fertility in Survivors after Hodgkin Lymphoma Treatment within the German Hodgkin Study Group HD13 to HD15 Trials. J Clin Oncol 31 (2013), 231-239.

34. Behringer, K.; Breuer, K.; Reineke, T.; et al. Secondary Amenorrhea after Hodgkin's Lymphoma Is Influenced by Age at Treatment, Stage of Disease, Chemotherapy Regimen, and the Use of Oral Contraceptives during Therapy: A Report from the German Hodgkin's Lymphoma Study Group. Journal of Clinical Oncology 23 (2005): 7555-7564.

35. Irene Su, H.; Kwan, B.; Whitcomb, B. W.; et al. Modeling Variation in the Reproductive Lifespan of Female Adolescent and Young Adult Cancer Survivors Using AMH. J Clin Endocrinol Metab 105 (2020): 2740-2751.

36. Silva, C.; Ribeiro Rama, A. C.; Reis Soares, S.; et al. Adverse Reproductive Health Outcomes in a Cohort of Young Women with Breast Cancer Exposed to Systemic Treatments. J Ovarian Res 12 (2019).

37. Fong, S. L.; Laven, J. S. E.; Hakvoort-Cammel, F. G. A. J.; et al. Assessment of Ovarian Reserve in Adult Childhood Cancer Survivors Using Anti-Müllerian Hormone. Human Reproduction 24 (2009): 982-990.

38. Chamani, I. J.; Gannon, A.; Connell, P. T.; et al. Dose-Dense Chemotherapy Regimen for Breast Cancer Associated with Significant Decline in Ovarian Reserve. J Adolesc Young Adult Oncol 13 (2024).

39. Chiarelli, A. M.; Marrett, L. D.; Darlington, G. Early Menopause and Infertility in Females after Treatment for Childhood Cancer Diagnosed in 1964-1988 in Ontario, Canada. Am J Epidemiol 150 (1999): 245-254.

40. Van Der Kaaij, M. A. E.; Heutte, N.; Meijnders, P.; et al. Premature Ovarian Failure and Fertility in Long-Term Survivors of Hodgkin's Lymphoma: A European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'ÉTude Des Lymphomes de l'Adulte Cohort Study. Journal of Clinical Oncology 30 (2012): 291-299.

41. De Bruin, M. L.; Huisbrink, J.; Hauptmann, M.; et al. Treatment-Related Risk Factors for Premature Menopause Following Hodgkin Lymphoma. Blood 111 (2008): 101–108.

42. Sklar, C. A.; Mertens, A. C.; Mitby, P.; et al. Premature Menopause in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. JNCI: Journal of the National Cancer Institute 98 (2006), 890-896.

43. Felicetti, F.; Castiglione, A.; Biasin, E.; et al. Effects of Treatments on Gonadal Function in Long-Term Survivors of Pediatric Hematologic Malignancies: A Cohort Study. Pediatr Blood Cancer 67 (2020).

44. Krawczuk-Rybak, M.; Płonowski, M.; Leszczyńska, E.; et al. The Influence of Different Intensity of Treatment on Hormonal Markers of Gonadal Function in Acute Lymphoblastic Leukemia Survivors. Hematol Oncol 37 (2019), 609-616.

45. Park, S. J.; Choi, J. Y.; Kang, H. J.; et al. Risk Factors for Treatment-Related Amenorrhea in Female Survivors of Childhood and Adolescent Cancer: 10-Year Experiences at Oncofertility Clinic in Korean Tertiary Center. J Adolesc Young Adult Oncol 13 (2024).

46. Beneventi, F.; Locatelli, E.; Giorgiani, G.; et al. Adolescent and Adult Uterine Volume and Uterine Artery Doppler Blood Flow among Subjects Treated with Bone Marrow Transplantation or Chemotherapy in Pediatric Age: A Case-Control Study. Fertil Steril 103 (2015), 455-461.

47. Barton, S. E.; Najita, J. S.; Ginsburg, E. S.; et al. Infertility,

Infertility Treatment, and Achievement of Pregnancy in Female Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study Cohort. Lancet Oncol 14 (2013): 873-881.

48. Melin, J.; Madanat-Harjuoja, L.; Heinävaara, S.; et al. Fertility Treatments among Female Cancer Survivors Giving Birth – a Finnish Register-Based Study. Acta Oncol (Madr) 56 (2017): 1089-1093.

49. Rautonen, J.; Koskimies, A. I.; Siimes, M. A. Vincristine Is Associated with the Risk of Azoospermia in Adult Male Survivors of Childhood Malignancies. Eur J Cancer 28 (1992): 1837-1841.

50. Kenney, L. B.; Laufer, M. R.; Grant, F. D.; et al. High Risk of Infertility and Long Term Gonadal Damage in Males Treated with High Dose Cyclophosphamide for Sarcoma during Childhood (2001).

51. Thomson, A. B.; Campbell, A. J.; Kelnar, C. J. H.; et al. Semen Quality and Spermatozoal DNA Integrity in Survivors of Childhood Cancer: A Case-Control Study. Lancet 360 (2002): 361–367.

52. Van Casteren, N. J.; Van Der Linden, G. H. M.; Hakvoort-Cammel, F. G. A. J.; et al. Effect of Childhood Cancer Treatment on Fertility Markers in Adult Male Long-Term Survivors. Pediatr Blood Cancer 52 (2009): 108–112.

53. Tromp, K.; Claessens, J. J. M.; Knijnenburg, S. L.; et al. Reproductive Status in Adult Male Long-Term Survivors of Childhood Cancer. Human Reproduction 26 (2011): 1775-1783.

54. Romerius, P.; Ståhl, O.; Moëll, C.; et al. High Risk of Azoospermia in Men Treated for Childhood Cancer. Int J Androl 34 (2011): 69–76.

55. Rendtorff, R.; Beyer, M.; Müller, A.; et al. Low Inhibin B Levels Alone Are Not a Reliable Marker of Dysfunctional Spermatogenesis in Childhood Cancer Survivors. Andrologia 44 (2012): 219–225.

56. Haavisto, A.; Lampic, C.; Wettergren, L.; et al. Reproductive Late Effects and Testosterone Replacement Therapy in Male Childhood Cancer Survivors: A Population-Based Study (the Fex-Can Study). Int J Cancer 154 (2024).

57. Namekawa, T.; Imamoto, T.; Kato, M.; et al. Testicular Function among Testicular Cancer Survivors Treated with Cisplatin-based Chemotherapy. Reprod Med Biol 15 (2016): 175.

58. Duca, Y.; Di Cataldo, A.; Russo, G.; et al. Testicular Function of Childhood Cancer Survivors: Who Is Worse? J Clin Med 8 (2019).

59. Beaud, H.; Albert, O.; Robaire, B.; et al. Sperm DNA Integrity in Adult Survivors of Paediatric Leukemia and Lymphoma: A Pilot Study on the Impact of Age and Type of Treatment. PLoS One 14 (2019).

60. Johnston, R. J.; Wallace, W. H. B. Normal Ovarian Function and Assessment of Ovarian Reserve in the Survivor of Childhood Cancer. Pediatr Blood Cancer 53 (2009), 296-302.

61. Definitions of Infertility and Recurrent Pregnancy Loss: A Committee Opinion. Fertil Steril 113 (2020): 533-535.

62. Lunsford, A. J.; Whelan, K.; McCormick, K.; et al. Antimüllerian Hormone as a Measure of Reproductive Function in Female Childhood Cancer Survivors. Fertil Steril 101 (1): 227–231.

63. Tournaye, H.; Dohle, G. R.; Barratt, C. L. R. Fertility Preservation in Men with Cancer. Lancet 384 (2014), 1295–1301.

64. Nelson, S. M.; Telfer, E. E.; Anderson, R. A. The Ageing Ovary and Uterus: New Biological Insights. Hum Reprod Update 19 (2013): 67-83.

65. Broekmans, F. J.; Soules, M. R.; Fauser, B. C. Ovarian Aging: Mechanisms and Clinical Consequences. Endocr Rev 30 (2009): 465-493.

66. Wu, F. C. W.; Tajar, A.; Beynon, J. M.; Pye, S. R.; et al. Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men. N Engl J Med 363 (2010), 123-135.

67. Feldman, H. A.; Longcope, C.; Derby, C. A.; et al. Age Trends in the Level of Serum Testosterone and Other Hormones in Middle-Aged Men: Longitudinal Results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 87 (2002): 589–598.

68. Burger, H. G.; Hale, G. E.; Robertson, D. M.; et al. A Review of Hormonal Changes during the Menopausal Transition: Focus on Findings from the Melbourne Women's Midlife Health Project. Hum Reprod Update 13 (2007): 559-565.

69. Zebrack, B. J.; Casillas, J.; Nohr, L.; et al. Fertility Issues for Young Adult Survivors of Childhood Cancer. Psychooncology 13 (2004), 689-699.

70. Gorman, J. R.; Su, H. I.; Roberts, S. C.; et al. Experiencing Reproductive Concerns as a Female Cancer Survivor Is Associated with Depression. Cancer 121 (2015): 935-942.

71. Armuand, G. M.; Wettergren, L.; Rodriguez-Wallberg, K. A.; et al. Desire for Children, Difficulties Achieving a Pregnancy, and Infertility Distress 3 to 7 Years after Cancer Diagnosis. Support Care Cancer 22 (2014): 2805–2812.

Deltour C, et al., Arch Intern Med Res 2024
DOI:10.26502/aimr.0186

72. Clasen, N. H. Z.; van der Perk, M. E. M.; Neggers, S. J. C. M. M.; et al. Experiences of Female Childhood Cancer Patients and Survivors Regarding Information and Counselling on Gonadotoxicity Risk and Fertility Preservation at Diagnosis: A Systematic Review. Cancers (Basel) 15 (2023).

73. Peccatori, F. A.; Azim, J. A.; Orecchia, R.; et al. Cancer, Pregnancy and Fertility: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. Annals of Oncology 24 (2013).

74. Mulder, R. L.; Font-Gonzalez, A.; Green, D. M.; et al. Fertility Preservation for Male Patients with Childhood, Adolescent, and Young Adult Cancer: Recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 22 (2021), e57–e67.

75. Mulder, R. L.; Font-Gonzalez, A.; Hudson, M. M.; et al. Fertility Preservation for Female Patients with Childhood, Adolescent, and Young Adult Cancer: Recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 22 (2021), e45–e56.