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# Reproductive ability in survivors of childhood, adolescent, and young adult Hodgkin lymphoma: a review

**Katja C.E. Drechsel [1,2,3,*], Maxime C.F. Pilon [1,2], Francis Stoutjesdijk [1,2], Salena Meivis [1,2], Linda J. Schoonmade [4], William Hamish B. Wallace [5], Eline van Dulmen-den Broeder [1], Auke Beishuizen [2,6], Gertjan J.L. Kaspers [1,2], Simone L. Broer [7], and Margreet A. Veening [1,2]**

[1]Pediatric Oncology, Cancer Center Amsterdam, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands [2]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands [3]Cancer Center Amsterdam, Amsterdam UMC, Location VUmc, VU Amsterdam, Amsterdam, The Netherlands [4]Medical Library, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands [5]Department of Haematology/Oncology, Royal Hospital for Sick Children, Edinburgh, UK [6]Department of Haematology/Oncology, Erasmus MC—Sophia Children's Hospital, Rotterdam, The Netherlands [7]Department of Reproductive Medicine & Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands

*Correspondence address. Pediatric Oncology, Cancer Center Amsterdam, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, 1007MB Amsterdam, The Netherlands; Princess Máxima Center for Pediatric Oncology, 3584 CS Utrecht, The Netherlands; Cancer Center Amsterdam, Amsterdam UMC, Location VUmc, VU Amsterdam, 1007 MB Amsterdam, Netherlands. E-mail: k.c.e.drechsel@amsterdamumc.nl https://orcid.org/0000-0001-9879-4678

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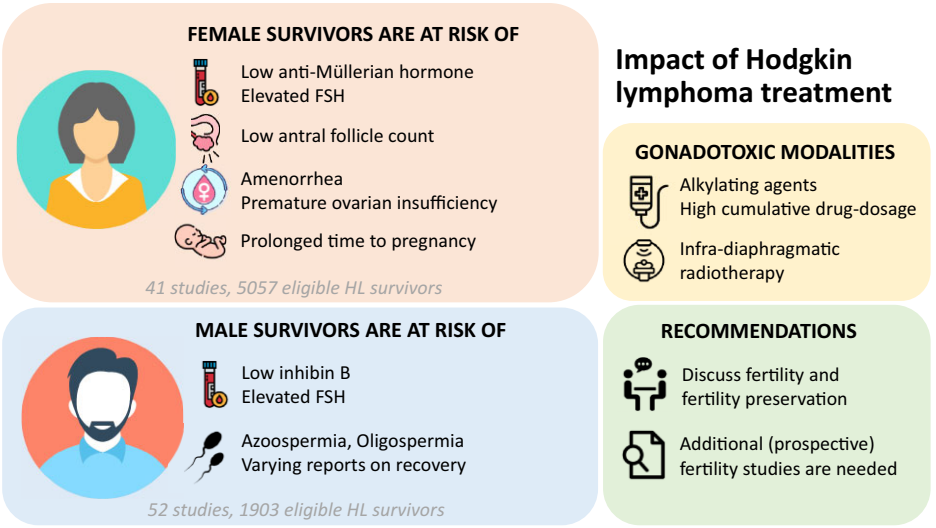
## GRAPHICAL ABSTRACT




**Effects of treatment at <25 years of age on reproductive markers in survivors of Hodgkin lymphoma (HL).**

**BACKGROUND:** Owing to a growing number of young and adolescent Hodgkin lymphoma (HL) survivors, awareness of (long-term) adverse effects of anticancer treatment increases. The risk of impaired reproductive ability is of great concern given its impact on quality of life. There is currently no review available on fertility after childhood HL treatment.

**OBJECTIVE AND RATIONALE:** The aim of this narrative review was to summarize existing literature on different aspects of reproductive function in male and female childhood, adolescent, and young adult HL survivors.

**SEARCH METHODS:** PubMed and EMBASE were searched for articles evaluating fertility in both male and female HL survivors aged <25 years at diagnosis. In females, anti-Müllerian hormone (AMH), antral follicle count, premature ovarian insufficiency (POI), acute ovarian failure, menstrual cycle, FSH, and pregnancy/live births were evaluated. In males, semen-analysis, serum FSH, inhibin B, LH, testosterone, and reports on pregnancy/live births were included. There was profound heterogeneity among studies and a lack of control groups; therefore, no meta-analyses could be performed. Results were presented descriptively and the quality of studies was not assessed individually.

**OUTCOMES:** After screening, 75 articles reporting on reproductive markers in childhood or adolescent HL survivors were included. Forty-one papers reported on 5057 female HL survivors. The incidence of POI was 6–34% (median 9%; seven studies). Signs of diminished ovarian reserve or impaired ovarian function were frequently seen (low AMH 55–59%; median 57%; two studies. elevated FSH 17–100%; median 53%; seven studies). Most survivors had regular menstrual cycles. Fifty-one studies assessed fertility in 1903 male HL survivors. Post-treatment azoospermia was highly prevalent (33–100%; median 75%; 29 studies). Long-term follow-up data were limited, but reports on recovery of semen up to 12 years post-treatment exist. FSH levels were often elevated with low inhibin B (elevated FSH 0–100%; median 51.5%; 26 studies. low inhibin B 19–50%; median 45%; three studies). LH and testosterone levels were less evidently affected (elevated LH 0–57%, median 17%; 21 studies and low testosterone 0–43%; median 6%; 15 studies). In both sexes, impaired reproductive ability was associated with a higher dose of cumulative chemotherapeutic agents and pelvic radiotherapy. The presence of abnormal markers before treatment indicated that the disease itself may also negatively affect reproductive function (Females: AMH<p10 9%; one study and Males: azoospermia 0–50%; median 10%; six studies). Reports on chance to achieve pregnancy during survivorship are reassuring, although studies had their limitations and the results are difficult to evaluate. In the end, a diminished ovarian reserve does not exclude the chance of a live birth, and males with aberrant markers may still be able to conceive.

**WIDER IMPLICATIONS:** This review substantiates the negative effect of HL treatment on gonadal function and therefore young HL survivors should be counseled regarding their future reproductive life, and fertility preservation should be considered. The current level of evidence is insufficient and additional trials on the effects of HL and (current) treatment regimens on reproductive function are needed. In this review, we make a recommendation on reproductive markers that could be assessed and the timing of (repeated) measurements.

**Key words:** Hodgkin lymphoma / childhood cancer / (future) fertility / reproductive ability / adverse effects / gonadotoxicity / azoospermia / premature ovarian insufficiency

# Introduction

Hodgkin lymphoma (HL) is a hematological malignancy, characterized by a bimodal age distribution at diagnosis with incidence peaks in young adulthood (15–35 years old) and after the age of 50 years. Over the past decades, HL treatment regimens have evolved gradually. Survival rates first improved when MOPP (mechlorethamine, oncovin (vincristine), procarbazine, and prednisolone) and ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) were introduced as a multi-agent strategies, supplemented by conventional radiotherapy. Subsequent follow-up data suggested high gonadotoxicity, and since then trials aim to replace gonadotoxic alkylating agents and reduce radiation doses and fields, without comprising effectivity rates. Current HL treatment is response- and risk adapted, and adult- and childhood HL patients are treated with distinct treatment protocols. The 5-year survival rate nowadays exceeds 90% in pediatric HL patients (Borchmann et al., 2012; Mauz-Körholz et al., 2022).

Still, administered chemotherapy and radiotherapy often cause toxicity with long lasting adverse effects, including increased risks of cardiovascular diseases and second malignancies that cause a substantially reduced life expectancy for HL survivors, when compared to the general population (van Leeuwen et al., 2000; Ng et al., 2002; Aleman et al., 2007; Myrehaug et al., 2008; Andersson et al., 2011; Swerdlow et al., 2011; Schaapveld et al., 2015; van Nimwegen et al., 2015; van Leeuwen and Ng, 2017; de Vries et al., 2021). Therapeutic effects that impede reproductive function are of great concern given their impact on future health and quality of life, particularly in young cancer survivors for whom parenthood is often among the most important future life goals (Carter et al., 2010; Canada and Schover, 2012; Benedict et al., 2016, 2018; Ellis et al., 2016; Johnson et al., 2018).

Anticancer treatment can damage the female gonads by inducing apoptosis of the primordial follicles, changes in vascularization of the ovaries, and cortical fibrosis, leading to atrophy (Meirow, 2000; Oktem and Oktay, 2007; Sonigo et al., 2019). Patients may experience (temporal) menstrual irregularities, climacteric symptoms, and hormonal disturbances but gonadal dysfunction may also lead to sub- or infertility because of ovarian failure and/or a shorter fertile lifespan because of the reduced number of primordial follicles (Spears et al., 2019).

In males, the deleterious effects of chemotherapy and radiotherapy primarily affect the germinal epithelium. Within the seminiferous epithelium of the testis, spermatogonial stem cells form the basis of spermatogenesis by a process of division and differentiation, which is initiated at the onset of puberty. Cytotoxic treatment and especially radiation may damage and deplete germ cells and differentiating spermatogonia, leading to a (temporary) cessation of spermatogenesis and diminished sperm quality (Brougham et al., 2003; Meistrich, 2013; Goossens et al., 2020). Potential recovery depends on survival of the spermatogonial stem cells, and if the entire pool is depleted, males are infertile (Goossens et al., 2020). Testosterone-producing Leydig cells are thought to be more resistant, but after high cumulative doses of anticancer drugs, Leydig cell dysfunction may also become apparent and hypoandrogenism may (although very uncommon) present as fatigue, impaired libido, premature osteoporosis, and metabolic disorders (Romerius et al., 2009; Kenney et al., 2012; Brignardello et al., 2016).

Problems with fertility do not become apparent until puberty or years thereafter. While the absence of puberty indicates infertility, the occurrence of pubertal development does not guarantee adequate gonadal function. Survivors may still have to deal with impaired reproductive ability and females may face a shortened fertile lifespan. Arguably, the ultimate proof of fertility is a live birth after pregnancy, but several markers are available to predict reproductive ability in (young) females and males as well.

In females, premature depletion of ovarian function is referred to as premature ovarian insufficiency (POI). POI is diagnosed in women with evidence of hypergonadotropic-hypogonadism in the setting of amenorrhea before the age of 40 years (Webber et al., 2016). Deterioration of ovarian function, meaning a diminished ovarian reserve, can be measured by ovarian reserve tests. The antral follicle count (AFC) and measurement of circulating anti-Müllerian hormone (AMH) are commonly used markers of ovarian reserve (Hansen et al., 2011; Anderson and Su, 2020). AFC, the number of visible antral follicles on a (transvaginal) ultrasound, reflects the size of the primordial follicle pool. AMH is produced in the granulosa cells of the ovary by the primary, secondary, pre-antral and antral follicles up to 8 mm in diameter, and these developing follicles also reflect the size of the remaining primordial follicle pool (Depmann et al., 2018).

In females, AMH levels are low or almost undetectable at birth and increase during childhood, with a peak during late puberty (Kelsey et al., 2011). In general, AMH levels rise up to the age of 25 years old and then start to decline. AFC and AMH naturally decrease during reproductive aging. Prior to disturbances in other hormones (e.g. FSH, estradiol, and inhibin B) or cycle length changes, a decrease in AMH can be seen, and AMH is predictive for timing of menopause (Broer et al., 2014).

AMH was introduced as a novel marker for reproductive lifespan in the 2010s (Rosen et al., 2012; Broer et al., 2014). Traditionally, studies referred to regularity of the menstrual cycle (with 'regular' defined as cycles within the range of 20–45 days) or increased serum FSH concentration (>10 IU/l) to evaluate gonadal function. However, FSH levels are strongly cycle dependent and values do not reflect ovarian reserve, nor can they individually reflect ovarian function (Broer et al., 2014).

Semen analysis is the gold standard to assess male fertility. Semen can be qualified and quantified, and lower limit reference values for concentration, motility, and morphology are published by the World Health Organization (Cooper et al., 2010). However, semen analysis can only be performed after puberty. The body of literature on (prepubertal) spermatogenial numbers in testicular tissue is growing (Masliukaite et al., 2016; Stukenborg et al., 2018a), but assessment of such counts in cancer patients is still in the context of (experimental) testicular biopsies and estimation of reproductive function in prepubertal boys depends on serum markers.

Testicular damage affects the levels of circulating hormones (Franchimont et al., 1972; Dhabhar et al., 1993; Mackie et al., 1996). Inhibin B is the active form of inhibin, a glycoprotein hormone produced by the testicular Sertoli cells. Inhibin B regulates FSH secretion, which further affects the hypothalamic–pituitary–gonadal axis. It is believed that low inhibin B reflects a decreased function of the seminiferous tubules (Robertson et al., 1988; Dhabhar et al., 1993; Jensen et al., 1997; Klingmüller and Haidl, 1997; Brugo-Olmedo et al., 2001). Generally, FSH serum levels >10 IU/l and/or inhibin B levels of <100 ng/l are considered to indicate damage to spermatogenesis in males (Lähteenmäki et al., 1999; Kelsey et al., 2017). In contrast, the

measurement of serum LH and testosterone as markers for fertility seems to be of limited value, although both hormones reflect Leydig cell function and testosterone plays a vital role in pubertal development and spermatogenesis (Smith and Walker, 2014; Keskin *et al.*, 2015).

The number of childhood and adolescent HL survivors grows, based on stable incidences combined with high survival rates. Over the recent decades, treatment protocols have rapidly evolved and awareness of the gonadotoxicity of anticancer treatment has increased. Fertility preservation programmes are initiated in effort to preserve fertility of (young) cancer patients receiving high-risk treatments (Mulder *et al.*, 2021a,b; van der Perk *et al.*, 2021).

Although (future) fertility after treatment for HL is discussed in an increasing number of studies, as far as we know no reviews of the literature are available. The aim of the current review was to summarize existing literature on different aspects of gonadal function and fertility in both female and male childhood, adolescent, and young adult survivors of HL. We aimed to: identify patient and treatment characteristics associated with an increased risk of impaired reproductive ability; provide personalized, risk-based information and counseling for patients on their future fertility; and identify patients that could benefit from fertility preservation at diagnosis, before start of treatment.

# Methods

## Search strategy

A comprehensive search was performed in the bibliographic databases PubMed and Embase.com, from inception to 2 December 2021, in collaboration with a medical librarian (L.J.S.). Search terms included controlled terms (MeSH in PubMed and Emtree in Embase) as well as free text terms. Search terms expressing 'Hodgkin lymphoma' were used in combination with search terms comprising 'treatment' and 'fertility'. The search was performed without date or language restrictions. A search filter was used to exclude animal studies, and case reports and congress abstracts were also excluded. The full search strategies for all databases can be found in Supplementary Data File S1. Duplicate articles were excluded (by L.J.S.) using Endnote X20.0.1 (Clarivatetm), following the Amsterdam Efficient Deduplication-method and the Bramer-method (Bramer *et al.*, 2016; Otten *et al.*, 2019).

## Study selection and data extraction

At least two reviewers (from M.C.F.P., E.v.D.-d.B., M.A.V., S.M., and K.C.E.D.) independently screened all potentially relevant titles and abstracts for eligibility using Covidence (Covidence systematic review software, 2022). Inconsistencies were discussed with a third (independent) reviewer.

Studies were included if they met the following criteria:

- study design; cohort studies, case-control studies, or randomized controlled trials (RCTs); either prospective, retrospective, or cross-sectional,
- study population; male and/or female HL patients/survivors OR childhood, young adult or adolescent cancer patients/survivors, aged <25 years at diagnosis, outcomes; evaluating fertility in a broad sense, reporting at least one of the following outcome measures;
- Males: semen analysis, serum markers of gonadal function (i.e. elevated FSH, low inhibin B, FSH/inhibin B ratio, elevated LH, low testosterone), pregnancy, or live birth rates;
- Females: markers of ovarian reserve (i.e. low AMH, low AFC), markers of ovarian failure (i.e. POI, acute ovarian failure (AOF), menstrual cycle characteristics (i.e. regular cycle, amenorrhea, oligomenorrhea), elevated serum FSH, and pregnancy or live birth rates).

Studies were excluded if they met any of the following the criteria:

- wrong publication type, i.e. case reports, case series, letters, animal studies, reviews, conference abstracts, guidelines,
- no full text available, or not available in English, German, French or Dutch language,
- did not report separate results for HL patients or there were <10 HL patients in total cohort for which results are reported separately,
- >25% of the study population was aged 25 years or older at diagnosis and there were no separate outcomes reported for age <25 years,
- age at diagnosis for HL unknown,
- co-treatment with GnRH analogues, and
- overlapping cohort (only the largest study was included).

## Data synthesis

Data on trial design and setting, study population, age at cancer diagnosis and time of study, follow-up period, and treatment characteristics were extracted by two reviewers (M.C.F.P. and K.C.E.D.) working independently, using a previously designed and piloted data extraction form (not shown).

In females, markers of ovarian reserve (AMH, AFC; pre- or post-treatment) and reports on POI were included as primary outcomes. All reports on premature ovarian failure or insufficiency before the age of 40 years, sometimes within papers referred to as non-surgical premature menopause, were defined as POI in this review. AOF, elevated serum (basal) FSH (pre- or post-treatment), menstrual cycle characteristics (i.e. regular cycle, amenorrhea, oligomenorrhea), and pregnancy or live birth rates (defined as prevalence or absolute number of pregnancies or live births, with or without ART) were included as secondary outcomes.

In males, primary outcomes comprised semen analysis pre- or post-treatment (i.e. semen volume, sperm concentration, total sperm count in ejaculate, classification azoospermia/(severe) oligospermia, normospermia, percentage progressive motility, percentage normal morphology, percentage vitality) and several serum markers of gonadal function (i.e. (basal) FSH, inhibin B, FSH/inhibin B ratio; pre- or post-treatment). Additional serum markers (i.e. (basal) LH, testosterone) and pregnancy and live birth rates were included as secondary outcomes.

In studies that did not report study characteristics for the eligible HL-subgroup specifically (i.e. aged <25 years at diagnosis), data were extracted for the entire cohort (e.g. in case of mixed cancer cohorts or studies that included older HL patients). The cutoff values used for increased or decreased markers were extracted if available. Commonly used definitions of markers of gonadal function and a list of abbreviations are included in Supplementary Table SI. If available,

reports on recovery of gonadal function and sequential analysis of markers in both males and females were extracted as well.

Owing to the profound heterogeneity in included studies, it was not possible to perform additional analyses. The present review is a narrative review and no structured critical appraisal was performed.

# Results

## Search results

The literature search generated a total of 6869 references: 2843 in PubMed and 4026 in Embase.com. After removing duplicates of references that were selected from more than one database, 4723 references remained. Records were screened and 834 full-text articles were assessed for eligibility. Of these, 74 articles were eligible for inclusion in this review. One additional study was added via citation screening. The flow chart of the search and selection process is presented in Fig. 1.

## Female HL survivors

Overall, there were 41 studies included that reported on fertility related outcomes in 5057 female childhood or adolescent HL survivors (Supplementary Table SII). Seventeen studies were cross-sectional, 10 were executed prospectively, and 14 were executed retrospectively. Most studies originated from the USA (n = 17), the UK (n = 5), the Netherlands (n = 5), and Italy (n = 4). The remaining 10 trials were initiated from Canada, Portugal, France, Germany, Poland, Slovenia, Sweden, Copenhagen, Tunisia, and Turkey. Studied populations often only comprised patients with HL, but in 11 papers the cohort included multiple childhood cancer diagnoses (mixed childhood cancer: MCC); in those papers, the results on gonadal markers were extracted for the subgroup of HL patients aged below 25 years. Patients were treated between 1940 and 2018. Administered chemotherapy-drugs as well as radiotherapy (dose and site) varied widely, and the included (abbreviated) HL-treatment protocols are listed in Supplementary Table SI. Seven studies mentioned that (some of) the included females had oophoropexy before radiotherapy. Median duration of follow-up or time until execution of a (cross-sectional) study ranged from a few

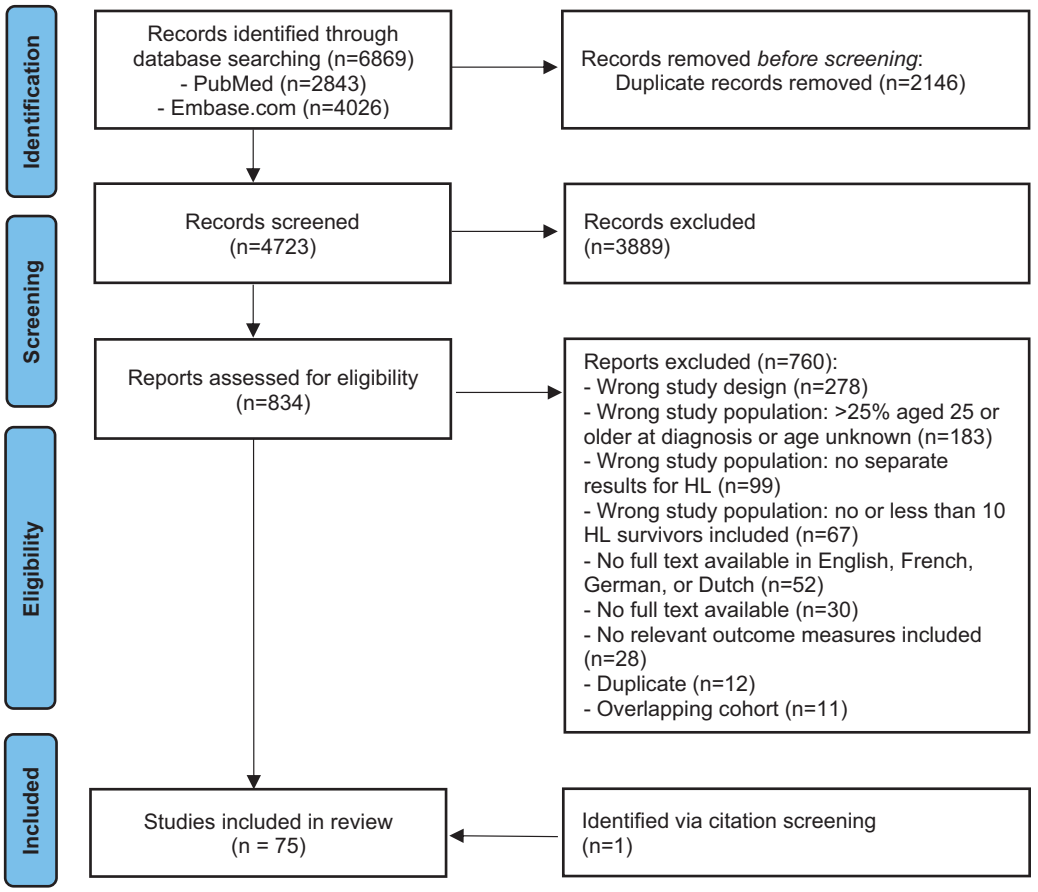



**Figure 1. Flow chart of literature database search results and exclusion of studies.** HL, Hodgkin lymphoma. Diagram adapted from Page *et al.* (2021).

years post-treatment up to 48 years. Results were compared to a control or reference group (healthy females or siblings) in 10 studies.

### *Anti-Müllerian hormone*

Six of the included studies reported on AMH. Low AMH serum levels in childhood and adolescent HL survivors were reported in three articles (91 patients) (van Beek *et al.*, 2007b; Charpentier *et al.*, 2014; van Dorp *et al.*, 2014). Of these, one article evaluated pre-treatment AMH serum levels in females with median age 6.6 years (range 0–17.4) and reported on nine (28%) females with 'low' AMH values, defined as <p10 percentile of healthy controls (van Dorp *et al.*, 2014). The other two studies evaluated AMH serum levels after a follow-up period of median ±11 years (range 1.4–25.1) after treatment. The studies compared AMH serum levels in female HL survivors aged 23–25 years old (range 18.2–40.4) to AMH values in healthy controls and found 55–59% of the study population to have low AMH (<14 pmol/l = 6.2 ng/ml or <95% CI of healthy controls), especially in those survivors treated with chemotherapy protocols including procarbazine (van Beek *et al.*, 2007b). In both studies, none of the patients had received pelvic radiotherapy. Three additional papers (89 patients) reported a significant decrease in AMH before and after treatment for HL (Krawczuk-Rybak *et al.*, 2013a; Berjeb *et al.*, 2020; Policiano *et al.*, 2020). A summary of results is presented in Table I and Supplementary Fig. S1.

### *Antral follicle count*

Only the paper by Policiano *et al.* (2020) reported AFC in HL survivors, and they mentioned a decrease in AFC post-treatment in comparison to values pre-treatment after a follow-up of ±2.8 years (44 patients, pre-treatment AFC 19 (interquartile range (IQR) 14–23), and post-treatment 10 (IQR 7–15), *P* value not given). Patients with an AFC below 6 or serum AMH below 0.84 ng/ml at baseline were excluded from this study.

### *Premature ovarian insufficiency and ovarian failure*

The number of female survivors with POI was reported in seven of the included studies (1516 patients) (Table II and Supplementary Fig. S1) (Green *et al.*, 1981; Sklar *et al.*, 2006; Zaletel *et al.*, 2010; van der Kaaij *et al.*, 2012b; Swerdlow *et al.*, 2014; Levine *et al.*, 2018; Felicetti *et al.*, 2020). The percentage of female HL survivors with signs of POI ranged from 6% to 34% (median 9%) and was especially high in patients receiving radiotherapy and BEAM (i.e. high-dose chemotherapy before autologous hemopoietic stem cell transplantation (HSCT)) (Sklar *et al.*, 2006; Swerdlow *et al.*, 2014). Long-term follow-up data were lacking. Only in one study the median age of included HL survivors at time of the study exceeded 40 years, while in two other studies the oldest patients at time of follow-up assessment were 24 and 29 years old.

Three additional studies (154 patients) reported on ovarian failure, without presenting an applied definition or classification (Ortin *et al.*, 1990; Hudson *et al.*, 1993; Mackie *et al.*, 1996). It could not be assumed that the term 'ovarian failure' was exclusively used to refer to POI and, therefore, results were presented separately. Nevertheless, reported incidences were comparable to reports on the incidence of POI (12–31% ovarian failure and 4–34% POI, respectively). All patients with ovarian failure in the study by Mackie *et al.* (1996) had received pelvic irradiation.

One study reported on AOF (553 patients) and stated that 12% of the included females reported never menstruating or ceased having spontaneous menses within 5 years after cancer diagnosis (Chemaitilly *et al.*, 2006). The occurrence of AOF was associated with age at cancer diagnosis >12 years old. Nevertheless, this study was a cross-sectional study, and potential cycle recovery was not evaluated. Gonadotrophin patterns were not assessed either.

### *Menstrual cycle*

Information on menstrual cycle of HL survivors was provided in 18 included studies (387 patients), see Supplementary Table SIII and Supplementary Fig. S1. Most studies reported that the majority of HL survivors developed or maintained normal and regular menstrual cycles (median percentage of HL survivors with regular cycle 100%, range 79–100%, nine studies; 168 patients) (Horning *et al.*, 1981; Whitehead *et al.*, 1982; Andrieu and Ochoa-Molina, 1983; Perrone *et al.*, 1989; Hudson *et al.*, 1993; Gözdasoglu *et al.*, 1995; Madsen *et al.*, 1995; Donaldson *et al.*, 2007; Zaletel *et al.*, 2010). Hudson *et al.* (1993) mentioned that three patients developed amenorrhea during therapy but resumed spontaneous menses 2–4 years after completion of therapy. Other articles reported on rates ranging from 0% to 71% (median 4%) of patients experiencing amenorrhea post-treatment (Wilimas *et al.*, 1980; Green *et al.*, 1981; Koziner *et al.*, 1986; Green and Hall, 1988; Madsen *et al.*, 1995; Mackie *et al.*, 1996; Brusamolino *et al.*, 2000; Zaletel *et al.*, 2010).

### *FSH*

Eight studies (155 patients) included elevated FSH serum levels in female HL survivors at follow-up as an outcome measurement (Green *et al.*, 1981; Perrone *et al.*, 1989; Mackie *et al.*, 1996; Papadakis *et al.*, 1999; van Beek *et al.*, 2007b; Zaletel *et al.*, 2010; Krawczuk-Rybak *et al.*, 2013a; Salih *et al.*, 2015). The percentage of patients with elevated FSH after a median follow-up of ±6 years (range 0–30) varied from 17% to 100%, median 53% (values above cutoff value 8–30 IU/l, or high in comparison to healthy controls or survivors of other types of childhood cancer). Elevated FSH values were observed more frequently in patients treated with procarbazine/MOPP and those treated with abdominal/pelvic radiotherapy (Green *et al.*, 1981; Papadakis *et al.*, 1999; van Beek *et al.*, 2007b; Zaletel *et al.*, 2010). Results on serial sampling were available in 14 patients from one study (Papadakis *et al.*, 1999). All patients were treated with procarbazine and cyclophosphamide, and none had received pelvic radiotherapy. Seven patients had elevated FSH values at time of first evaluation, in three patients the values remained abnormal up to 18 years post-diagnosis and in the other four patients FSH concentrations normalized over time (at 2, 3, 4, and 9 years post-diagnosis). Serum FSH levels of the remaining seven patients remained normal throughout the entire assessment period. Results are summarized in Supplementary Table SIV and Supplementary Fig. S1.

### *Pregnancy/live birth*

There were 19 studies that reported at least one pregnancy or live birth in 1262 out of the 2388 (53%) included female HL survivors (Supplementary Table SV). Pivetta *et al.* (2011) reported a significantly lower ratio of observed (O) to expected (E) number of liveborn children for 110 married/cohabitant female HL survivors, in comparison to general population, ratio 0.53; 95% CI 0.42–0.64. However, the

**Table I Anti-Müllerian hormone and antral follicle count in childhood or adolescent females diagnosed with Hodgkin lymphoma.**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| | | | ***Pre-treatment*** | | | |
| van Dorp *et al.*, 2014 | 32 | 6.6 (0–17.4) | NA | NA | NA | Pre-treatment, n = 9/32 (28%) patients with low AMH (i.e. <p10 percentile of healthy controls) |
| | | | ***Post-treatment*** | | | |
| Charpentier *et al.*, 2014 | 29 | 11.9 (1.8–17.3) | 23.3 (18.2–34.2) | 11.5 (1.4–25.1)* | Chemo: n.s.<br>No pelvic RT | n = 16/29 (55%) females with low AMH (i.e. <14 pmol/l) |
| van Beek *et al.*, 2007b | 30 | 14.0 (5.0–17.2) | 25 (19.2–40.4) | 11.6 (5.7–24.5) | Chemo: ABVD, EBVD, MOPP<br>No pelvic RT | n = 10/17 (59%) patients with low AMH (i.e. <95% CI of healthy controls)<br>• *Survivors without MOPP had higher AMH levels compared to survivors treated with MOPP (1.40 ug/l vs 0.39 ug/l, P = 0.01)*<br>• *All women with increased FSH levels had decreased AMH levels* |
| | | | ***Decrease in AMH or AFC pre-/post-treatment*** | | | |
| Berjeb *et al.*, 2020 | 32 | 21.6 ± 4.4 | n.s. | (1.3–1.5) | Chemo: BEACOPP, DHAOX, ABVD<br>No pelvic RT | Significant decrease in AMH before and after chemotherapy. 2.30 ± 1.96 and 1.54±1.96 ng/ml; *P* = 0.002<br>In n = 7/32 (22%) women, AMH values were higher after chemotherapy, when compared to AMH values pre-treatment |
| Krawczuk-Rybak *et al.*, 2013a | 13 | 14 ± 3.45 | 20.1 ± 3.5 | (6–10) | Chemo: MVPP + BDOPA<br>Pelvic RT: n = 8/13 (62%), 15 Gy | Significant decrease in AMH before and after treatment 2.96 ng/ml ± 2.05 and 1.26 ng/ml ± 0.84, *P* = 0.001 |
| Policiano *et al.*, 2020 | 44 | 22.6 (IQR 18.8–26.4) | n.s. | 2.8 | Chemo: ABVD<br>No pelvic RT | Decrease in AMH before and after treatment 2.2 ng/ml (IQR 1.4–4.4 ng/ml) and 1.3 ng/ml (IQR 0.9–2.5 ng/ml), *P* not given<br>Decrease in AFC before and after treatment 19 (IQR 14–23), and 10 (IQR 7–15), *P* not given<br>Patients with AFC <6 or AMH <0.84 ng/ml at baseline were excluded |

*Follow-up period defined as years off treatment.

ABVD, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine; AMH, anti-Müllerian hormone; AFC, antral follicle count; BDOPA, Bleomycin, Dacarbazine, Vincristine (Oncovin), Adriamycin, Prednisone; BEACOPP, Bleomycin, Etoposide, Adiamycin (Doxorubicin), Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone; Chemo, chemotherapy; DHAOX, Dexamethasone, high-dose Cytarabine, and Oxaliplatin; EBVD, Epirubicin, Bleomycin, Vinblastine, Dacarbazine; Gy, Gray; IQR, interquartile range; MOPP, Mechlorethamine, Vincristine (Oncovin), Procarbazine, Prednisone; MVPP, Mechlorethamine, Vinblastine, Procarbazine, Prednisone; NA, not applicable; n.s., not specified; N, number; RT, radiotherapy.

Age at diagnosis and time of study reported in median years (range) or mean ± SD.

The number of patients that received pelvic radiotherapy as (part of their) cancer treatment is reported. If mentioned in the article (pelvic) radiation dosage is specified.

**Table II Premature ovarian insufficiency and (acute) ovarian failure in childhood or adolescent females diagnosed with Hodgkin lymphoma.**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| ***Premature ovarian insufficiency (POI)*** | | | | | | |
| Felicetti *et al.*, 2020 | 33 | <18 | 24.7 (21.5–28.3) | n.s. | Chemo: n.s.<br>Pelvic RT: n = 21/131 (16%)[1] | n = 2/33 (6%) patients with POI, defined as amenorrhea and consistently low 17beta-estradiol levels and elevated gonadotropin levels |
| Green *et al.*, 1981 | 7 | 14.6 (11.2–16.8 | 18.5 (15.4–24.2) | 2.6 (1.3–5.6) | Chemo: MOPP, CVPP<br>Pelvic RT: n = 5/7 (71%), 544–4180 rads<br>Oophoropexy: n = 5/7 (71%) | n = 2/7 (29%) patients with gonadotropin patterns consistent with ovarian failure (not defined) |
| Levine *et al.*, 2018 | 348 | 6 (0–20) | 35 (18–58) | n.s. | Chemo: n.s.<br>Pelvic RT: n = 51/348 (15%) | n = 56/348 (16%) patients with non-surgical premature menopause, defined as sustained menses cessation occurring for 6 months beginning 5 years after the cancer diagnosis but before age 40 years that was not due to pregnancy, surgery, or medications |
| Sklar *et al.*, 2006 | 404 | 7 (0–20) | 9 (18–50) | n.s. | Chemo: n.s.<br>Pelvic RT: n.s. | n = 38/404 (9%) with NSPM, defined as not experienced a spontaneous menses for at least 6 months. Other causes (e.g. pregnancy; use of agents such as injectable progesterone and gonadotropin-releasing hormone analogs) had been excluded.<br>• *Exposure to higher doses of ovarian irradiation was associated with an increased risk of NSPM*<br>• *In total cohort of MCC: survivors with NSPM were older at diagnosis and follow-up and were more likely to be diagnosed with HL* |
| Swerdlow *et al.*, 2014 | 508 | (0–25) | n.s. | 17.8 (0.3–48.4) | Chemo: ABVD, BEAM, ChlVPP, LOPP, MVPP, MOPP<br>Pelvic RT: at least n = 33/2127 (2%), >5 Gy | n = 173/508 (34%) with menopause <age 40 years.<br>• *Menopause generally occurred sooner after ovarian radiotherapy (62.5% within 5 years of ≥5 Gy treatment, overall cumulative risk 81%) and BEAM therapy (50.9% within 5 years, overall cumulative risk 75%)* |
| van der Kaaij *et al.*, 2012b | 192 | (15–24) | 49 (25–76) | 15 (5–45) | Chemo: ABVD, EBVP, MOPP, ABV, BEACOPP<br>Pelvic RT: n = 136/575 (24%)[1] | n = 14/192 (7%) patients with non-surgical premature menopsause, defined as cessation of menstruation at least 1 year before the date of survey before 40, in absence of pregnancy, breastfeeding, continuous use of progestogens, or other medication causing menorrhea or surgical removal uterus/ovaries<br>Cumulative risk of POI was 17% (95% CI 9–30%) |
| Zaletel *et al.*, 2010 | 24 | 13 (3–16) | 21 (13–34) | 10 (4–27) | Chemo: MOPP, LOPP, ABV(D), COPP(A), OPPA<br>Pelvic RT: n = 4/24 (17%), 30 (22–45) Gy | n = 1/24 (4%) with early menopause (no age cutoff defined)<br>n = 1/24 (4%) with primary amenorrhea |
| ***Ovarian failure (undefined) and acute ovarian failure (AOF)*** | | | | | | |
| Chemaitilly *et al.*, 2006 | 553 | (0–20) | n.s. | n.s. | Chemo: n.s.<br>Pelvic RT: n.s. | n = 66/553 (12%) survivors who self-reported never menstruating or reported that they had ceased having spontaneous menses within 5 years after cancer diagnosis (in article referred to as: AOF, acute ovarian failure) |
| Hudson *et al.*, 1993 | 36 | 14.6 (4.2–20) | n.s. | 4 (1–9.7) | Chemo: COP-ABVD<br>Pelvic RT: n = 18/42 (43%), 15–20 Gy<br>Oophoropexy: n.s. | n = 6/36 (17%) with ovarian failure (not defined)<br>• *6/18 (33%) in patients who received pelvic irradiation*<br>• *0/17 (0%) in patients who did not receive pelvic irradiation* |

(continued)

**Table II Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Mackie *et al.*, 1996 | 32 | 13.0 (9.0–15.2) | n.s. | 4.3 (1.9–11.5)* | Chemo: ChlVPP<br>No Pelvic RT | n = 10/32 (31%) with 'symptomatic' ovarian failure (not defined) |
| Ortin *et al.*, 1990 | 86 | 13 (12–15) | n.s. | 9 (up to 26) | Chemo: MOPP, PAVe, ABVD, VBM<br>Pelvic RT: n = 28/86 (33%), 15–45 Gy<br>Oophoropexy: n = 52/92 (57%) | n = 11/86 (13%) with ovarian failure (not defined) |

*Follow-up period defined as years off treatment.

[!]Reported number only available within total cohort (i.e. not specified for HL diagnosis or age-subgroup).

ABV, Adriamycin (Doxorubicin), Bleomycin, Vinblastine; ABVD, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine; AOF, acute ovarian failure; BEACOPP, Bleomycin, Etoposide, Adiamycin (Doxorubicin), Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone; BEAM, BCNU (bis-chloroethylnitrosourea), Etoposide, Cytarabine, Melphalan; Chemo, chemotherapy; ChlVPP, Chlorambucil, Vinblastine, Procarbazine, Prednisone; COP-ABVD; Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine; COPP, Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone; CVPP, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone; EBVP, Epirubicin, Bleomycin, Vinblastine, Prednisone; Gy, gray; HL, Hodgkin lymphoma; LOPP, Chlorambucil, Vincristine (Oncovin), Procarbazine, Prednisone; MOPP, Mechlorethamine, Vincristine (Oncovin), Procarbazine, Prednisone; MVPP, Mechlorethamine, Vinblastine, Procarbazine, Prednisone; NA, not applicable; n.s., not specified; N, number; OPPA, Vincristine (Oncovin), Prednisone, Procarbazine, Adriamycin (Doxorubicin); PAVe, Procarbazine, Alkeran, Velban; POI, premature ovarian insufficiency; RT, radiotherapy; VBM, Velban, Bleomycin, Methotrexate.

Age at diagnosis and time of study reported in median years (range) or mean ± SD.

The number of patients that received pelvic radiotherapy as (part of their) cancer treatment is reported. If mentioned, (pelvic) radiation dosage is included. If oophoropexy is mentioned in the paper, number of patients is specified.

ratio was not significantly different when all surviving women of the studied population were included (i.e. married, never married and unknown marital status, n = 271, ratio 0.88; 95% CI 0.71–1.08) (Pivetta *et al.*, 2011). Brämswig *et al.* (2015) stated that the proportion of women HL survivors having children was comparable to the German general population, except for the 66 HL survivors aged 40–44 years old, in whom the proportion of mothers was significantly lower (61% of 66 HL survivors versus 78% of 2 847 000 women, $P = 0.001$) (Brämswig *et al.*, 2015): the study observed no statistically significant difference in parenthood among females aged 45–49 years old. Two additional studies specifically mentioned they only included female HL survivors who attempted to become pregnant. In the study by van der Kaaij *et al.* (2012a), 176 out of the 218 (81%) females gave birth to at least one child after treatment for HL. Horning *et al.* (1981) reported 28 pregnancies in 20 of the 26 (77%) included women who attempted to become pregnant, with a median time to pregnancy of 42 months (3–100 months). Only three studies mentioned whether females used ART to become pregnant. The number of pregnancies achieved via IUI or IVF were n = 4/176, n = 2/17 and n = 1/10 (Papadakis *et al.*, 1999; van Beek *et al.*, 2007b; van der Kaaij *et al.*, 2012a, respectively). One paper assessed parenthood according to several treatment- and diagnosis related factors and stated that pelvic radiation appeared to have a substantial effect on the hazard ratio (HR) for parenthood (HR 0.66 95% CI 0.48–0.90, $P = 0.006$) (Brämswig *et al.*, 2015).

## Male HL survivors

### *Included studies*

A total of 52 studies, reporting on 1903 males diagnosed with HL before the age of 25 years, were included in this review. An overview of included studies is provided in Supplementary Table SVI. Studies were cross-sectional (n = 26) or had a retrospective (n = 20) or prospective (n = 6) design, there were no RCTs included in this review. Trials originated from 18 different countries, including the USA (n = 13), the UK (n = 7), Italy (n = 6), the Netherlands (n = 5), Germany (n = 5), France (n = 3), Sweden (n = 2), and others (Brazil, Uganda, India, Israel, Iran, Turkey, Slovenia, Czech Republic, Denmark, Poland, and Switzerland—all n = 1). Of the 52 studies, 32 included only HL patients, 1 non-Hodgkin lymphoma (NHL) and HL patients, 16 MCC patients, 2 included childhood hematological malignancy patients, and 1 included a mixed cancer cohort with patients of all ages. In all, 12 studies used a control group or reference cohort in their analyses. Patients were treated with varying HL treatment protocols, between 1940 and 2017.

### *Semen analysis*

A large number of the studies reported on sperm quality pre-treatment (12 studies, 324 patients) and/or post-treatment (30 studies, 809 patients). Most studies reported on (quantitative) sperm quality by defining sperm concentration in HL patients as 'normospermic', 'oligospermic', or 'azoospermic' (i.e. sperm concentrations of >15 million/ml, 5–15 million/ml, and 0 sperm/ml, respectively). Some articles reported on qualitative sperm deterioration by mentioning asthenozoospermia (abnormal motility) and theratospermia (abnormal morphology). Results are summarized in Table III and Supplementary Fig. S2.

Most studies detected a high incidence of abnormal semen (pre-treatment azoospermia range 0–50%; median 10%; six studies, pre-treatment oligospermia range 39–68%; median 55%; three studies, post-treatment azoospermia range 33–100%; median 75%; 29 studies, post-treatment oligospermia range 0–33%; median 17.5%; 14 studies). Treatment with high doses of alkylating agents, such as procarbazine and cyclophosphamide, appeared to be a risk factor for both decreased sperm counts and quality, and negative effects on semen appeared to be even stronger when alkylating chemotherapy was combined with testicular irradiation (Green and Hall, 1988; Dhabhar *et al.*, 1993; Shafford *et al.*, 1993; Heikens *et al.*, 1996; van den Berg *et al.*, 2004; Hobbie *et al.*, 2005; van Beek *et al.*, 2007a; Romerius *et al.*, 2010). Some studies specifically evaluated semen quality in patients with elevated FSH, and most of these patients were azoospermic (Brämswig *et al.*, 1990; Gözdasoglu *et al.*, 1995; Zaletel *et al.*, 2010). One study compared pre-treatment semen storage in cancer patients and reported, in addition to abnormal semen characteristics, a trend toward fewer straws (and thus lower sperm volume produced) among patients with HL ($P = 0.051$) compared to other patients with an indication for sperm cryopreservation (i.e. sarcoma, testicular cancer, NHL, other malignant hemopathies or other/non-oncological indications) (Adam *et al.*, 2020).

Most studies evaluated semen quality in HL survivors at a single time point. Three studies evaluated the semen quality both pre- and post-cancer treatment (Heikens *et al.*, 1996; van Casteren *et al.*, 2008; Laddaga *et al.*, 2022). The study by Laddaga *et al.* (2022) reported that 8 out of 11 males (73%) had sperm abnormalities at time of diagnosis (i.e. oligospermia, azoospermia, and/or theratospermia), four of these males (50%) had abnormal sperm counts at 54 months (range 26–137 months) after treatment. Three of these patients had undergone allogeneic or autologous HSCT which, according to the study results, was associated with severe fertility impairment in terms of sperm motility (74% motility at diagnosis versus 22% motility after HSCT in the entire study cohort with both young and older HL patients, $P = 0.025$) (Laddaga *et al.*, 2022). The other two studies reported abnormal (mean) semen analysis characteristics pre-treatment (Heikens *et al*: mean sperm count 3.4 ± 5.5 million, van Casteren *et al*: mean sperm concentration 12.0 (SEM 5.1) million/ml with low volume and motility), and 50–63% of the HL survivors had azoospermia post-treatment (Heikens *et al.*, 1996; van Casteren *et al.*, 2008).

In total, four papers mentioned results of sequential semen analysis for years after treatment (da Cunha *et al.*, 1984; Anselmo *et al.* 1990; Ortin *et al.* 1990; Heikens *et al.*, 1996). Three studies reported on recovery of spermatogenesis in males receiving six cycles of MOPP (Anselmo *et al.* 1990; Ortin *et al.* 1990; Heikens *et al.*, 1996). Heikens *et al.* observed no recovery of spermatogenesis up to 20 years after treatment in 19 patients (two received pelvic irradiation), while 3 out of 9 (33%) azoospermatic patients aged <25 years old at diagnosis had late recovery in the paper by Anselmo *et al.* (at 30, 57, 108 months post-treatment, respectively) (Anselmo *et al.* 1990; Heikens *et al.*, 1996). In a study by Ortin *et al.* (1990) two azoospermic boys (one received supra-diaphragmatic radiation) had late recovery (both 12 years after treatment, and they both successfully fathered a child). The semen analysis of all other 10 boys with azoospermia (four received pelvic radiation) showed no recovery during follow-up (up to 11 years after treatment). In the paper by da Cunha *et al.* (1984) recovery of semen to normozoospermic counts (at 3 and 9 years post-treatment) was only observed in two patients with initial oligospermia

**Table III** Semen analysis in childhood or adolescent males diagnosed with Hodgkin lymphoma.

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| | | | | | ***Pre-treatment*** | |
| Adam *et al.*, 2020 | 24 | 17.2 ± 1.7 | NA | NA | NA | Volume 2.0 ± 1.3, concentration 39.7 ± 37.0, sperm count 97 ± 103<br>progressive motility 39.8 ± 24.7, total motile sperm count 19.9 ± 24.5<br>azoospermic patients were excluded (number n.s.)<br>There was a trend towards fewer straws among HL patients, when compared to other cancer diagnoses, $P = 0.051$ |
| Bahadur *et al.*, 2002 | 36 | 16.44 | NA | NA | NA | Volume 1.4 (SEM0.2), sperm count 55.6 (SEM7.3)<br>overall motility (%abc) 51.7 (SEM 2.8) |
| DiNofia *et al.*, 2017 | 54 | 16.9 ± 2.6 | NA | NA | NA | n = 8/54 (15%) azoospermia |
| Ginsberg *et al.*, 2008 | 13 | 16.1 ± 0.5 | NA | NA | NA | n = 0/13 (0%) azoospermia. n = 5/13 (39%) oligospermia |
| Hagenäs *et al.*, 2010 | 19 | 16.4 (12.7–17.9) | NA | NA | NA | Volume 1.7 (0.1–5.9), concentration 8.5 (0–86), sperm count 7 (0–243),<br>progressive motility 35% (0–86%), total motile sperm 3.2 (0–186)<br>n = 1/19 (5%) azoospermia, n = 13/19 (68%) oligospermia |
| Heikens *et al.*, 1996 | 19 | 11.0 (5–15) | NA | NA | NA | Sperm count 3.4 ± 5.5 |
| Keene *et al.*, 2012 | 38 | 16.2 ± 1.2 | NA | NA | NA | Volume 0.5 (0.4–1.1), concentration 15.0 (1–56)<br>progressive motility 20% (13–29%) |
| Krawczuk-Rybak *et al.*, 2012 | 10 | 15–18 | NA | NA | NA | Sperm count range 30–175, progressive motility 10–45%<br>n = 0/4 (0%) azoospermia, n = 3/4 (75%) theratospermia, n = 4/4 (100%) asthenozoospermia. |
| Laddaga *et al.*, 2022 | 11 | (17–24) | NA | NA | NA | n = 8/11 (73%) with dyspermia (6× oligospermia, 5× azoospermia, 1× theratospermia). |
| Menon *et al.*, 2009 | 30 | 17.8 ± 0.1 (13–20) | NA | NA | NA | Volume 2.3 ± 0.2, sperm count 29.9 ± 5.7<br>progressive motility 29.3 ± 2.5%<br>n = 4/8 (50%) azoospermia |
| Paoli *et al.*, 2016 | 50 | 15.8 ± 1.1 | NA | NA | NA | Volume 1.8 ± 1.3, concentration 63.7 ± 69.9, sperm count 96.8 ± 94.7<br>progressive motility 39.6 ± 15.3%<br>Azoospermic patients were excluded (number n.s.) |
| van Casteren *et al.*, 2008 | 20 | 16.3 (SEM 0.3) | NA | NA | NA | Volume 0.8 (0.2), concentration 12.0 (SEM 5.1)<br>motility 29.5% (SEM 3.9) |
| | | | | | ***Post-treatment*** | |
| Anselmo *et al.* 1990 | 20 | 20 (16–24) | n.s. | (0.5–1) | Chemo: MOPP, ABVD, MOPP/ABVD<br>Pelvic RT: n.s. | n = 16/20 (80%) azoospermia<br>n = 2/20 (10%) oligospermia.<br>n = 3 azoospermatic patients (treated with 6 cycles of MOPP) and n = 2 oligospermatic patients (treated with 6 cycles of ABVD) had late recovery at 30, 57, 108, 18, and 19 months post-treatment, respectively |
| Aubier *et al.*, 1989 | 10 | 10 (8–15) | n.s. | 9 (1–20) | Chemo: MOPP, VELBE, ABVD<br>No pelvic RT | n = 7/10 (70%) azoospermia |

(continued)

**Table III Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Ben Arush *et al.*, 2000 | 12 | 13.7 (2.1–16.4) | 22 (14.8–29.3) | 9.8 (4–19) | Chemo: MOPP, ABVD<br>Pelvic RT: n = 4/20[1] (20%), 1650–4000 rad[1] | n = 7/12 (58%) azoospermia.<br>n = 4/12 (33%) oligospermia |
| Bordallo *et al.*, 2004 | 21 | 10 (6–19) | 18 (17–23) | (3–11) | Chemo: C-MOPP, ABV<br>No pelvic RT | n = 11/18 (61%) azoospermia<br>n = 4/18 (22%) oligospermia |
| Brämswig *et al.*, 1990 | 75 | 12.44 ± 2.1 | 17.24 ± 2.19 | 4.3 ± 1.9 | Chemo: OPPA, COPP<br>Pelvic RT: n = 10/75 (13%), 18–40 Gy | n = 4/4 (100%) azoospermia in patients with elevated FSH |
| da Cunha *et al.*, 1984 | 12 | 20 (15–24) | n.s. | 4 (1.2–10.6) | Chemo: MOPP<br>Pelvic RT: n = 4/12 (33%), 150–425 rad | n = 5/12 (42%) azoospermia<br>n = 3/12 (25%) oligospermia<br>n = 2 azoospermic patients became oligospermic at 14 and 127 months post-treatment. n = 2 oligospermic patients recovered to sperm counts within normal range at 41 and 103 months post-treatment. All patients were treated with no more than 3 MOPP courses, 1 had received pelvic irradiation. |
| Dhabhar *et al.*, 1993 | 26 | 12 (4–15) | 17 (15–23) | 6.1 (2.3–11) | Chemo: COPP, ABVD, MOPP<br>No pelvic RT | n = 18/18 (100%) azoospermia |
| Donaldson *et al.*, 2007 | 75 | 13.3 (3.6–21) | n.s. | 9.6 (1.7–15.0) | Chemo: VAMP.<br>Pelvic RT: n.s. | n = 1/1 (100%) azoospermia |
| Gözdasoglu *et al.*, 1995 | 10 | n.s. | 18 (11–29) | (5–24) | Chemo: C-MOPP<br>Pelvic RT: n.s. | n = 4/4 (100%) azoospermia in patients with elevated FSH |
| Green and Hall, 1988 | 48 | 14.9 (5.1–19.9) | (18.1–42.3) | n.s. | Chemo: n.s.<br>Pelvic RT: n = 18/48 (38%) | n = 8/8 (100%) azoospermia |
| Heikens *et al.*, 1996 | 19 | 11.0 (5–15) | 19 (16–27) | 14 (13–20) | Chemo: MOPP<br>Pelvic RT: n = 2/19 (11%), 20–25 Gy | n = 12/19 (63%) azoospermia<br>n = 6/19 (32%) oligospermia<br>No recovery of spermatogenesis up to 20 years after treatment (n = 19 patients, treated with 6 cycles of MOPP, 2 received pelvic irradiation). |
| Hobbie *et al.*, 2005 | 11 | 13.2 (6–19) | 21 (18–31) | 6.5 (1.5–21) | Chemo: COPP-ABV<br>No pelvic RT | n = 7/11 (64%) azoospermia.<br>n = 2/11 (18%) oligospermia |
| Jaffe *et al.*, 1988 | 13 | 11 (6–15) | 22 (20–27) | 12 (5–15) | Chemo: COPP, MOPP<br>Pelvic RT: n = 13/13 (100%), 37–399 rad | n = 9/12 (75%) azoospermia.<br>n = 2/12 (17%) oligospermia |
| Koziner *et al.*, 1986 | 11 | 21 (9–29) | n.s. | 3 (0.8–2.4) | Chemo: MOPP.<br>Pelvic RT: n.s. | n = 8/11 (73%) azoospermia |
| Kruseová *et al.*, 2021 | 81 | 13.7 (0.1–19.1) | 23.6 (14.9–40.3) | 11.6 (5.1–32) | Chemo: n.s.<br>Pelvic RT: n = 26/143[1] (18%), 24.8 (15–40) Gy[1] | n = 60/81 (74%) with spermatogenesis damage (i.e. azoospermia, oligozoospermia or asthenozoospermia) |
| Laddaga *et al.*, 2022 | 11 | (17–24) | n.s. | 8.6 (4.4–14) | Chemo: ABVD<br>No pelvic RT | n = 4/11 (36%) with dyspermia (i.e. n = 3 oligospermia, n = 4 azoospermia, n = 1 theratospermia) |
| Mackie *et al.*, 1996 | 46 | 12.2 (8.2–15.3) | n.s. | 6 (2.5–11.1)* | Chemo: ChlVPP<br>No Pelvic RT | n = 7/7 (100%) azoospermia |
| Müller *et al.*, 1996 | 13 | 14 (3–17) | 21 (19–34) | 8 (1–18) | Chemo: CPP<br>Pelvic RT: n = n.s., 2–50 cGy | n = 6/6 (100%) azoospermia. |

(continued)

**Table III Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Ortin *et al.*, 1990 | 20 | 13 (12–15) | n.s. | 9 (up to 26) | Chemo: MOPP, PAVe, ABVD, VBM<br>Pelvic RT: n = 12/20 (60%), 20–44 Gy | n = 11/19 (59%) azoospermia<br>n = 3/19 (16%) oligospermia<br>2 boys had late recovery (one had normal sperm counts, 12 years post-treatment, one was azoospermic up to 10 years post-treatment, but successfully fathered a child 12 years after treatment). The semen analysis of the remaining 10 boys (with azoospermia showed no recovery during follow-up (up to 14 years after treatment)). All boys were treated with 6 cycles of MOPP, 4 were irradiated in the pelvic area. |
| Papadakis *et al.*, 1999 | 36 | 13.0 (2.4–22.6) | 22.3 (15.1–32.5) | 6.8 (2.0–19.3)* | Chemo: MDP<br>Pelvic RT: n = 6/36 (17%) | n = 2/2 (100%) azoospermia |
| Perrone *et al.*, 1989 | 7 | 9.0 (2.4–12.0) | 10.8 (3.0–18.0) | 1.2 (0.2–6.5) | Chemo: ABVD, MOPP<br>Pelvic RT: n = 2/7 (29%), 2500 rad | n = 3/3 (100%) azoospermia |
| Rafsanjani *et al.*, 2007 | 33 | 9 (5–15) | 19 (17–29) | 7 (2–20)* | Chemo: MOPP, ABVD<br>No pelvic RT | n = 27/33 (82%) azoospermia<br>n = 2/33 (6%) oligospermia |
| Relander *et al.*, 2000 | 11 | 13 (6–16) | n.s. | 11.4 (6.3–22.2) | Chemo: MOPP, MVPP, ABVD<br>Pelvic RT: at least n = 5/11 (45%), 40 Gy | n = 3/9 (33%) azoospermia<br>n = 0/9 (0%) oligospermia |
| Romerius *et al.*, 2010 | 19 | 10 (0.1–17) | 29 (20–46) | >4* | Chemo: n.s.<br>Pelvic RT: n.s. | n = 10/19 (53%) azoospermia |
| Shafford *et al.*, 1993 | 40 | n.s. | >16 | >6* | Chemo: ChlVPP, MOPP, MVPP, COPP, ABVD, PAVE, CCNU<br>Pelvic RT: n = 10/40 (25%), 2250–3500 cGy | n = 11/13 (85%) azoospermia,<br>n = 1/13 (8%) oligospermia |
| van Beek *et al.*, 2007a | 56 | 11.4 (3.7–15.9) | 27.0 (17.7–42.6) | 15.5 (5.6–30.2) | Chemo: ABVD, EBVD, MOPP<br>No pelvic RT | n = 9/21 (43%) azoospermia<br>n = 4/21 (19%) oligospermia<br>• *n = 9/17 (53%) azoospermia, n = 4/17(24%) oligospermia MOPP+ patients.*<br>• *n = 0/4 (0%) azoospermia/oligospermia in MOPP-*<br>Mean sperm concentration 49.1 (26–63) MOPP− (n = 4), and 1.1 (0–72) MOPP+ (n = 17) |
| van Casteren *et al.*, 2008 | 20 | 16.3 (SEM 0.3) | n.s. | 3.4 (0.8–14.0) | Chemo: n.s.<br>Pelvic RT: n.s. | n = 2/4 (50%) azoospermia. |
| van den Berg *et al.*, 2004 | 33 | 11.8 (3.8–17.2) | n.s. | 11.3 (0.5–24) | Chemo: MOPP, ABVD<br>Pelvic RT: n.s. | n = 9/13 (69%) azoospermia<br>n = 1/13 (8%) oligospermia<br>• *n = 8/10 (80%) azoospermia, n = 1/10 (10%) oligospermia in MOPP-group.*<br>• *n = 0/1 (0%) azoospermia in ABVD group*<br>• *n = 1/2 (50%) azoospermia in ABVD-MOPP group* |

(continued)

**Table III Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Whitehead *et al.*, 1982 | 15 | 11.2 (4.8–14.8) | n.s. | 3.3 (0,7–8)* | Chemo: MOPP, MVPP, ABVD.<br>Pelvic RT: n = 5/17 (29%), 100–300 cGy dose received by testes | n = 6/6 (100%) azoospermia |
| Zaletel *et al.*, 2010 | 40 | 13 (3–16) | 21 (13–34) | 10 (4–27) | Chemo: MOPP, LOPP, ABV(D), COPP(A), OPPA<br>Pelvic RT: n = 11/40 (28%), 30 (22–45) Gy | n = 6/6 (100%) azoospermia in males with primary hypogonadism (defined as basal serum FSH and/or LH level above the normal upper limit and exaggerated response after the administration of LH-RH. Gonadotropin releasing hormone) |

*Follow-up period defined as years off treatment.

[1]Reported number only available within total cohort (i.e. not specified for HL diagnosis or age-subgroup).

ABV, Adriamycin (Doxorubicin), Bleomycin, Vinblastine; ABVD, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine; CCNU, Chlorambucil, Etoposide; Chemo, chemotherapy; CHIVPP, Chlorambucil, Vinblastine, Procarbazine, Prednisone; C-MOPP, Cyclophosphamide, Nitrogen mustard, Vincristine (Oncovin), Procarbazine, Prednisone; COPP, Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone; CPP, Cetuximab, Paclitaxel, Cisplatin; EBVD, Epirubicin, Bleomycin, Vinblastine, Dacarbazine; Gy, gray; LOPP, Chlorambucil, Vincristine (Oncovin), Procarbazine, Prednisone; MDP, Adriamycin (Doxorubicin), Procarbazine, Prednisone, Vincristine (Oncovin), Cyclophosphamide; MOPP, Mechlorethamine, Vincristine (Oncovin), Procarbazine, Prednisone; MVPP, Mechlorethamine, Vinblastine, Procarbazine, Prednisone; NA, not applicable; n.s., not specified; N, number; OPPA, Vincristine (Oncovin), Prednisone, Procarbazine, Adriamycin (Doxorubicin); PAVE, Prednisolone, Adriamycin (Doxorubicin), Vinblastine, Etoposide; PAVe, Procarbazine, Alkeran, Velban; RT, radiotherapy; VAMP, Vincristine (Oncovin), Adriamycin (Doxorubicin), Methotrexate, Prednisone; VBM, Velban, Bleomycin, Methotrexate; VELBE, Vinblastine.

Age at diagnosis and time of study reported in median years (range) or mean ± SD.

The number of patients that received pelvic radiotherapy as (part of their) cancer treatment is reported. If mentioned, (pelvic) radiation dosage is included.

Reference values for semen analysis are summarized in Supplementary Table SI.

post-treatment who had received no more than three MOPP courses. Two patients treated with six courses ABVD had a relatively faster normalization of oligospermia, at 18 and 19 months post-treatment, respectively (Anselmo et al. 1990).

### FSH

A total of 28 included studies (738 patients) reported on (elevated) serum FSH levels in male HL patients or survivors (Table IV and Supplementary Fig. S2). One assessed pre-treatment serum FSH levels in 10 boys and reported a significantly higher mean FSH concentration in patients diagnosed with HL, when compared to healthy controls (6.3 ± 3.6 mIU/ml versus 4.6 ± 2.2 mIU/ml, respectively, $P = 0.05$) (Krawczuk-Rybak et al., 2012).

Among the eligible studies, the reported percentage of patients with elevated FSH ranged from 0% to 100% (median 51.5%). Nine studies used the generally accepted cutoff value of 10 IU/L to determine high FSH serum level, indicating damage to spermatogenesis (Sherins et al., 1978; Hassel et al., 1991; Heikens et al., 1996; Mackie et al., 1996; Müller et al., 1996; van den Berg et al., 2004; Servitzoglou et al., 2015; Brignardello et al., 2016; Felicetti et al., 2020). The other studies used higher cutoff values (i.e. >14, >15, >16, or >18 IU/l), lower cutoff values (i.e. >5, >6, or >8 IU/l), >2 SD of controls or did not mention the definition of elevated FSH.

In the study that reported no HL survivors with elevated FSH concentrations (0%), patients had received only two cycles of chemotherapy (OEPA: Vincristine (Oncovin), Etoposide, Prednisone, Adriamycin (Doxorubicin)) (Schellong, 1998). FSH was especially higher in boys who received multiple courses of procarbazine-containing chemotherapy regimens, boys who were late-pubertal or young adults in comparison to younger boys, and boys who had HL at a more advanced stage and received more intensive treatment protocols (Sherins et al., 1978; Green et al., 1981; Whitehead et al., 1982; Brämswig et al., 1990; Gerres et al., 1998; van den Berg et al., 2004; van Beek et al., 2007a).

Two studies mentioned there was no recovery of elevated serum FSH over time (up to 8.2 and 17 years follow-up, respectively) (Papadakis et al., 1999; Shafford et al. 1993). Two other studies observed normalization of FSH during follow-up in a few subjects (in 1 out 4 survivors and 2 out of 20 survivors, respectively) (Whitehead et al., 1982; Servitzoglou et al., 2015).

### Inhibin B

Five papers (182 patients) reported on inhibin B serum levels in HL patients (Table IV and Supplementary Fig. S2). Krawczuk-Rybak et al. (2012) detected significantly lower mean inhibin B concentration in newly diagnosed HL patients when compared to healthy controls (100.4 ± 67.5 ng/L versus 153.6 ± 71.4 ng/L, respectively, $P = 0.03$). The percentage of patients with low inhibin B (serum concentration <100 pg/ml was considered low) after treatment ranged from 19% to 50% (median 45%). Van Beek et al. observed that median FSH and LH values were significantly higher, and inhibin B levels significantly lower in patients treated with MOPP, when compared to patients that did not receive MOPP ($P = 0.01$). However, only inhibin B (not FSH or LH) serum levels showed an independent correlation with sperm concentration ($r = 0.86$; $P < 0.001$), suggesting that the measurement of inhibin B serum levels might be favored over other serum markers as being representative of male gonadal function (van Beek et al., 2007a).

Only one of the included studies mentioned the inhibin B/FSH ratio. Within this study, the median inhibin B/FSH ratio was lower in HL survivors when compared to controls (31 (3.8–267.9) in HL survivors versus 142.1 (47.6–767.3) in healthy controls, $P = 0.0002$, respectively) (Bordallo et al., 2004).

### LH

One study reported on LH levels pre-treatment, and mean serum LH values were significantly higher in HL patients when compared to healthy controls (5.9 ± 4.0 mIU/ml in 10 HL patients versus 3.6 ± 1.8 mIU/ml in 14 controls, respectively, $P = 0.05$) (Krawczuk-Rybak et al., 2012).

A total of 21 studies (528 patients) assessed the percentage of HL survivors with elevated LH serum concentrations (Supplementary Table SVII and Supplementary Fig. S2). Applied cutoff values to determine elevated concentrations varied widely (i.e. >3 up to >30 IU/l, >2 SD of controls, or not specified). Overall, the reported percentage of patients with elevated LH levels ranged from 0% to 59% (median 17%). The study by Servitzoglou et al. (2015) mentioned that a significantly higher proportion of patients with elevated LH levels had received abdominal radiotherapy, when compared to patients exhibiting normal LH levels (n = 6/7 (85%) versus n = 17/42 (40%), $P = 0.03$, respectively). Another study found that median LH levels were significantly higher in patients treated with MOPP when compared to patients receiving ABVD or EBVD (Epirubicin, Bleomycin, Vinblastine, Dacarbazine) (5.9 U/l (range 1.68–15.0, 40 patients) versus 2.5 U/l (range 1.2–9.0, 16 patients), $P = 0.01$) (van Beek et al., 2007a). Interestingly, a study by Ben Arush and colleagues mentioned that four HL survivors (33%) had low LH serum concentrations (<5 IU/L) post-treatment, while none of the 12 patients had elevated serum concentrations after treatment (Ben Arush et al., 2000).

A single study mentioned the results of sequential LH serum sampling during follow-up. LH concentrations normalized in two patients with initial high LH levels, and in eight other patients LH levels were initially within the normal reference limits but subsequently became elevated over time (Shafford et al., 1993).

### Testosterone

Most studies reported that serum testosterone concentrations in HL survivors were within normal range. One paper studied pre-treatment serum testosterone levels and reported no statistically significant difference between newly diagnosed HL patients and healthy boys (466.0 ± 67.5 ng/dl versus 466.8 ± 242.2 ng/dl, $P$ not given) (Krawczuk-Rybak et al., 2012). The percentage of patients with low testosterone values after treatment ranged from 0% to 43% (median 9%); 15 studies, 339 patients. Most studies used cutoff values close to 9–12 IU/l, but some studies applied much lower thresholds (e.g. <3 ng/dl = ±0.1 IU/l). Two studies stated that HL survivors sometimes had (relatively) high testosterone levels (Ben Arush et al.: n = 4/12 (33%) with testosterone levels >35 nmol/l post-treatment, Gerres et al.: mean testosterone levels were higher in 45 HL survivors when compared to 37 controls, $P$ not given) (Gerres et al., 1998; Ben Arush et al., 2000). Data on testosterone levels are presented in Supplementary Table SVII and Supplementary Fig. S2.

**Table IV** Serum FSH and inhibin B in childhood or adolescent males diagnosed with Hodgkin lymphoma.

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| | | | ***Pre-treatment*** | | | |
| Krawczuk-Rybak *et al.*, 2012 | 10 | 15–18 | NA | NA | NA | Significantly higher mean FSH value in HL patients when compared to healthy controls (6.3 ± 3.6 mIU/ml vs 4.6 ± 2.2 mIU/ml, $P = 0.05$). Significantly lower mean inhibin B concentration in HL patients when compared to healthy controls (100.4 ± 67.5 ng/l vs 153.6 ± 71.4 ng/l, $P = 0.03$). |
| | | | ***Post-treatment*** | | | |
| Aubier *et al.*, 1989 | 10 | 10 (8–15) | n.s. | 9 (1–20) | Chemo: MOPP, VELBE, ABVD<br>No pelvic RT | n = 4/4 (100%) with elevated FSH (i.e. >5 mcl/ml) |
| Ben Arush *et al.*, 2000 | 12 | 13.7 (2.1–16.4) | 22 (14.8–29.3) | 9.8 (4.0–19.0) | Chemo: MOPP, ABVD<br>Pelvic RT: n = 4/20[1] (20%) 1650–4000 rad[1] | n = 8/12 (67%) with elevated FSH (i.e. >14 mU/ml) |
| Bordallo *et al.*, 2004 | 21 | 10 (6–19) | 18 (17–23) | (3–11) | Chemo: C-MOPP, ABV<br>No pelvic RT | n = 15/21 (71%) with elevated FSH (i.e. >2 SD of control)<br>n = 4/21 (19%) with low inhibin B (i.e. <100 pg/ml)<br>Median IB/FSH ratio was lower in HL survivors when compared to controls (31 (3.8–267.9) in HL survivors versus 142.1 (47.6–767.3) in healthy controls, $P = 0.0002$, respectively) |
| Brämswig *et al.*, 1990 | 75 | 12.4 ± 2.1 | 17.2 ± 2.2 | 4.3 ± 1.9 | Chemo: OPPA, COPP<br>Pelvic RT: n = 10/75 (13%), 18–40 Gy | n = 26/65 (40%) with elevated FSH (i.e. >2 SD of controls) |
| Brignardello *et al.*, 2016 | 40 | <18 | n.s. | 14.01 | Chemo: n.s.<br>Pelvic RT: n.s. | n = 20/40 (50%) with elevated FSH (i.e. >10 IU/l) and low Inhibin B (<100 pg/ml) |
| Dhabhar *et al.*, 1993 | 26 | 12 (4–15) | 17 (15–23) | 6.1 (2.3–11) | Chemo: COPP, ABVD, MOPP<br>No pelvic RT | n = 14/23 (61%) with elevated FSH (i.e. >500 ng/ml) |
| Felicetti *et al.*, 2020 | 55 | <18 | 24.6 (21.8–29.4) | n.s. | Chemo: n.s.<br>Pelvic RT: n = 32/196[1] (16%) | n = 25/55 (45%) with elevated FSH (i.e. >10 IU/l) and low Inhibin B (i.e. <100 pg/ml) |
| Gerres *et al.*, 1998 | 46 | 14.9 ± 1.5 | n.s. | 11.7 ± 1.2 | Chemo: OEPA, COPP<br>No pelvic RT | n = 7/45 (16%) with elevated FSH (i.e. >2 SD of controls) |
| Gözdasoglu *et al.*, 1995 | 10 | n.s. | 18 (11–29) | (5–24) | Chemo: C-MOPP<br>Pelvic RT: n.s. | n = 4/10 (40%) with elevated FSH (i.e. >2 SD of controls) |
| Green *et al.*, 1981 | 17 | 12.1 (5.4–16.8) | 16.3 (8.3–24.4) | 3.4 (0.5–8.2) | Chemo: MOPP, CVPP, ABVD, BOPP<br>Pelvic RT: n = 9/17 (53%), 105–1090 rads | n = 11/17 (65%) with elevated FSH (i.e. >16 mU/ml) |
| Hassel *et al.*, 1991 | 25 | 13.6 ± 1.2 | 16.2 ± 1.2 | 2.4 (0.5–3.8) | Chemo: OPA, COMP<br>Pelvic RT: n.s. | n = 0/25 (0%) with elevated FSH (i.e. >10 IU/l) |

(continued)

**Table IV Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Heikens *et al.*, 1996 | 19 | 11.0 (5–15) | 19 (16–27) | 14 (13–20) | Chemo: MOPP<br>Pelvic RT: n = 2/19 (11%), 20–25 Gy | n = 15/19 (79%) with elevated FSH (i.e. >10 IU/l) |
| Hobbie *et al.*, 2005 | 11 | 13.2 (6–19) | 21 (18–31) | 6.5 (1.5–21) | Chemo: COPP-ABV<br>No pelvic RT | n = 5/11 (45%) with elevated FSH (i.e. >8 mIU/ml) |
| Mackie *et al.*, 1996 | 46 | 12.2 (8.2–15.3) | n.s. | 6 (2.5–11.1)* | Chemo: ChlVPP<br>No Pelvic RT | n = 41/46 (89%) with elevated FSH (i.e. >10 IU/l) |
| Müller *et al.*, 1996 | 13 | 14 (3–17) | 21 (19–34) | 8 (1–18) | Chemo: CPP<br>Pelvic RT: n = n.s., 2–50 cGy | n = 4/6 (66%) with elevated FSH (i.e. >10 IU/l) |
| Ortin *et al.*, 1990 | 20 | 13 (12–15) | n.s. | 9 (up to 26) | Chemo: MOPP, PAVe, ABVD, VBM<br>Pelvic RT: n = 12/20 (60%), 20–44 Gy | n = 7/10 (70%) with elevated FSH (i.e. >18 mIU/ml) |
| Papadakis *et al.*, 1999 | 36 | 13.0 (2.4–22.6) | 22.3 (15.1–32.5) | 6.8 (2.0–19.3)* | Chemo: MDP<br>Pelvic RT: n = 6/36 (17%), dose n.s. | n = 18/36 (50%) with elevated FSH (cutoff n.s.)<br>Serial sampling: 3 patients with normal FSH levels remained normal over time, in 3 patients with elevated FSH concentrations, values remained abnormal over a period ranging from 1.1 to 8.2 years post-treatment. |
| Perrone *et al.*, 1989 | 7 | 9.0 (2.4–12.0) | 10.8 (3.0–18.0) | 1.2 (0.2–6.5) | Chemo: ABVD, MOPP<br>Pelvic RT: n = 2/7 (29%), 2500 rad | n = 2/7 (29%) with elevated FSH (i.e. >2 SD of controls) |
| Rafsanjani *et al.*, 2007 | 33 | 9 (5–15) | 19 (17–29) | 7 (2–20)* | Chemo: MOPP, ABVD<br>No pelvic RT | n = 6/33 (18%) with elevated FSH (>15 mIU/ml) |
| Schellong, 1998 | 31 | 13 | >15 | >4 | Chemo: OPPA, OEPA, COPP<br>Pelvic RT: n.s. | n = 0/31 (0%) with elevated FSH (cutoff n.s.), in patients who received only 2 cycles OEPA |
| Servitzoglou *et al.*, 2015 | 50 | 10.8 (2.1–17.3) | 21.1 (17.0–30.4) | 9.3 (2.0–22.4)* | Chemo: MOPP, ABVD, ABVP, OPPA, COPP<br>Pelvic RT: n = 24/171[1] (14%) | n = 20/45 (44%) with elevated FSH (i.e. >10 IU/l)<br>Of the patients with elevated FSH, 2 patients had a significant decrease in FSH serum concentrations over time. In one of the patients, FSH levels decreased from 11.0 to 4.6 IU/l, 6.3–10 years post-treatment. In the other patient, FSH levels decreased from 16.0 to 5.8 IU/l, 5.4–9 years post-treatment. |
| Shafford *et al.*, 1993 | 40 | n.s. | >16 | >6* | Chemo: ChlVPP, MOPP, MVPP, COPP, ABVD, PAVE, CCNU<br>Pelvic RT: n = 10/40 (25%), 2250–3500 cGy | n = 26/28 (93%) with elevated FSH (>8 u $l^{-1}$) of patients who had chemotherapy. Of these, three pre-pubertal bots initially had normal FSH levels, which subsequently became elevated post-puberty<br>FSH levels remained elevated up to 17 years from end of therapy. |
| Sherins *et al.*, 1978 | 15 | (3–16) | n.s. | >2 | Chemo: MOPP<br>Pelvic RT: n.s. | n = 8/15 (53%) with elevated FSH (i.e. >10 IU/l)<br>• *n = 8/9 (89%) in pubertal boys with gynecomastia*<br>• *n = 0/6 (0%) in pre-pubertal boys* |

(continued)

**Table IV Continued**

| Study | N patients | Age at diagnosis (years) | Age at time of study (years) | Follow-up (years) | Treatment | Outcome |
|---|---|---|---|---|---|---|
| van Beek *et al.*, 2007a | 56 | 11.4 (3.7–15.9) | 27.0 (17.7–42.6) | 15.5 (5.6–30.2) | Chemo: ABVD, EBVD, MOPP<br>No pelvic RT | • *Median FSH values were significantly higher in patients treated with MOPP when compared to patients that did not receive MOPP (MOPP+ 16.8 U/l (range 1.3–51, 40 patients) versus MOPP− 3.0 U/l (range 1.7–6.0, 16 patients), P = 0.01).*<br>• *Median inhibin B levels were significantly lower in patients treated with MOPP when compared to patients that did not receive MOPP (MOPP+ 16.5 ng/l (range 0.0–173.0, 26 patients) versus MOPP− 144.0 ng/l (range 93.0–274.0, 12 patients), P = 0.01)* |
| van den Berg *et al.*, 2004 | 33 | 11.8 (3.8–17.2) | n.s. | 11.3 (0.5–24) | Chemo: MOPP, ABVD<br>Pelvic RT: n.s. | n = 14/33 (42%) with elevated FSH (i.e. >10 IU/l).<br>• *n = 11/13 (85%) MOPP group.*<br>• *n = 0/10 (0%) ABVD group.*<br>• *n = 3/10 (30%) ABVD-MOPP group* |
| Whitehead *et al.*, 1982 | 15 | 11.2 (4.8–14.8) | n.s. | 3.3 (0,7–8)* | Chemo: MOPP, MVPP, ABVD<br>Pelvic RT: *n* = 5/17 (29%), 100–300 cGy dose received by testes | *n* = 10/18* (56%) with elevated FSH (cutoff n.s., in text, within figures depicting basal and peak FSH concentrations, normal range of values are shown, the following cutoff values appears to be used: prepuberal and early puberty ±4 mU/ml, late pubertal ±7 mU.ml).<br>• *n* = 0/4 (0%) pre-pubertal,<br>• *n* = 2/4 (50%) early puberty,<br>• *n* = 8/10 (80%) late pubertal/adult<br>One out of 4 subjects with multiple measurements had initially a raised FSH concentration and a normal FSH level on subsequent testing.<br>*Some subjects had multiple measurements. There were no separate results available per participant. |
| Zaletel *et al.*, 2010 | 40 | 13 (3–16) | 21 (13–34) | 10 (4–27) | Chemo: MOPP, LOPP, ABV(D), COPP(A), OPPA<br>Pelvic RT: *n* = 11/40 (28%), 30 (22–45) Gy | *n* = 24/40 (60%) with elevated FSH (within paper referred to as 'germinal epithelium damage', cutoff n.s.)<br>*n* = 20/40 (50%) with primary hypogonadism (i.e. increased basal serum FSH/LH) |

*Follow-up period defined as years off treatment.
[I]Reported number only available within total cohort (i.e. not specified for HL diagnosis or age-subgroup).
ABV, Adriamycin (Doxorubicin), Bleomycin, Vinblastine; ABVD, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine; ABVP, Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Prednisone; BOPP, 1,3-bis(2-chloroethyl)-l-nitrosourea, Vincristine (Oncovin), Procarbazine, Prednisone; CCNU, Chlorambucil, Etoposide; Chemo, chemotherapy; CHIVPP, Chlorambucil, Vinblastine, Procarbazine, Prednisone; C-MOPP, Cyclophosphamide, Nitrogen mustard, Vincristine (Oncovin), Procarbazine, Prednisone; COMP, CCNU (Chlorambucil, Etoposide), Vincristine (Oncovin), Amethopterine, Procarbazine; COPP, Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone; CPP, Cetuximab, Paclitaxel, Cisplatin; CVPP, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone; EBVD, Epirubicin, Bleomycin, Vinblastine, Dacarbazine; Gy, gray; LOPP, Chlorambucil, Vincristine (Oncovin), Procarbazine, Prednisone; MDP, Adriamycin (Doxorubicin), Procarbazine, Prednisone, Vincristine (Oncovin), Cyclophosphamide; MOPP, Mechlorethamine, Vincristine (Oncovin), Procarbazine, Prednisone; MVPP, Mechlorethamine, Vinblastine, Procarbazine, Prednisone; NA, not applicable; n.s., not specified; N, number; OEPA, Vincristine (Oncovin), Etoposide, Prednisone, Adriamycin (Doxorubicin); OPA, Vincristine (Oncovin) Prednisone, Adriamycin (Doxorubicin); OPPA, Vincristine (Oncovin), Prednisone, Procarbazine, Adriamycin (Doxorubicin); PAVE, Prednisolone, Adriamycin (Doxorubicin), Vinblastine, Etoposide; PAVe, Procarbazine, Alkeran, Velban; RT, radiotherapy; VBM, Velban, Bleomycin, Methotrexate; VELBE, Vinblastine.
Age at diagnosis and time of study reported in median years (range) or mean ± SD.
The number of patients that received pelvic radiotherapy as (part of their) cancer treatment is reported. If mentioned, (pelvic) radiation dosage is included.

*Pregnancy/live birth*

In total, 13 of the included studies reported that 374 out of the 755 (50%) male childhood or adolescent HL survivors fathered a (biological) child. The study by Zaletel *et al.* (2010) specifically evaluated the number of males with signs of germinal epithelium damage (i.e. elevated FSH concentrations) having children (n = 5/24, 21%). Reulen *et al.* (2009) found no significant variation in odds ratio for live births by type of cancer, exposure to chemotherapy, or gonadal irradiation (odds for live birth 1.2 (95% CI: 0.9–1.8) in females, 0.9 (95% CI: 0.5–1.6) in males).

In studies that reported results of pre-treatment semen analysis, semen samples were retrieved for cryobanking in an effort to preserve fertility. Laddaga *et al* (2022) mentioned that none of the 11 males used their stored sperm after a median follow-up of 8.6 years (range 4.4–14 years, males were aged 17–24 years at diagnosis). None of these males achieved pregnancy, but it is unknown whether they even attempted pregnancy. None of the other included studies reported on the use of stored semen.

The results are summarized in Supplementary Table SVIII.

# Discussion

In this review, markers of gonadal function and fertility in female and male childhood and adolescent HL survivors were evaluated. Aberrant concentrations of reproductive hormone serum markers, risk of (premature) ovarian insufficiency in females, and abnormal semen analyses in males mark the risk of gonadotoxicity after exposure to (high) doses of chemotherapy and radiotherapy. An overview of the results is presented in Table V.

## Female HL survivors

Results show that female HL survivors are at increased risk of POI (6–34% of HL survivors had POI, median 9%; seven studies; 1516 patients) in comparison to healthy controls but owing to the few studies available, personalized treatments, and heterogeneity in the applied definition of POI, it is difficult to express the risk in odds or relative risk for individual patients. The studies evaluated young cancer survivors and the follow-up period was often relatively short, meaning that POI could still occur in the coming years and the stated incidence of POI could be underestimated.

The diagnosis of POI is definite. Recommendations on initial assessment and management of females with POI are established in the international ESHRE guidelines (Webber *et al.*, 2016). Hormone replacement treatment can provide relief of vasomotor symptoms, such as hot flushes or night sweats, but there is currently no proven treatment to restore ovarian function in women with POI and the chance of having a biological child is minimal. Therefore, the timely recognition of patients 'at risk' of comprised reproductive potential at a young age is crucial, as this will give these women the possibility to expedite their plans to become pregnant or opt for fertility preservation. However, reproductive staging in cancer survivors is complicated as adverse effects of treatment may be transitory (Harlow *et al.*, 2012).

AOF with temporary cessation of menses is normal during chemotherapy. Only one of the included articles specifically reported on AOF, finding that 12% of the survivors had ceased spontaneous menses within 5 years of diagnosis, but long-term follow-up data were lacking (Chemaitilly *et al.*, 2006). In most other papers, the majority of HL survivors self-reported regular menstrual cycles during follow-up (median follow-up ±5 years after treatment; 79–100% with regular cycle; median 100%; nine studies; 168 patients; 0–71% with amenorrhea; median 4%; 13 studies; 240 patients). The resumption of menstruation after therapy may be reassuring, but it remains uncertain for how long the cycle will be ovulatory. A regular cycle after cancer-treatment at a young age does not guarantee future fertility and these women may still be at increased risk of POI.

Increased serum FSH levels in female HL survivors were frequently reported (17–100% with elevated FSH; median 53%; seven studies; 132 patients), which may be useful to help recognize the preliminary 'phase' of POI, also known as incipient ovarian failure. However, serum FSH levels rise relatively late and, when compared to FSH, assessment of AMH appears to be a better predictor of the remaining ovarian reserve after anticancer treatments (van Beek *et al.*, 2007b; Bedoschi *et al.*, 2016). Usually, an immense initial decline in AMH is seen directly after chemotherapy, which indicates damage to the granulosa cells of the developing follicles (Anderson and Su, 2020; Anderson *et al.*, 2022). Subsequent recovery of AMH levels varies greatly, and measurement of AMH concentration over time may help to determine treatment gonadotoxicity, predict ovarian reserve and diagnose (permanent) ovarian insufficiency (Krawczuk-Rybak *et al.*, 2013b; Oktem *et al.*, 2018; Anderson *et al.*, 2022). In a study by Berjeb *et al.* (2020) a significant drop in AMH was observed at 6 months post-chemotherapy, and in three out of five HL patients a subsequent recovery of AMH was detected but in the other two patients AMH serum levels became even lower in the year thereafter. All patients were treated with BEACOPP (Bleomycin, Etoposide, Adiamycin (Doxorubicin), Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone), but detailed information on treatment received as well as baseline characteristics (including age) were not provided. In another study that followed AMH levels up to 24 months post-treatment in HL and NHL patients (up to 35 years old), varying recovery patterns were observed as well (Decanter *et al.*, 2021). In general, patients receiving ABVD (n = 67) had an earlier and more pronounced increase of AMH levels when compared to patients receiving higher doses of alkylating agents (n = 55). In this study, patients receiving ABVD showed pre-treatment AMH levels after ±6 months, while none of the patients treated with the previously mentioned regimens had reached pre-treatment AMH levels during follow-up (Decanter *et al.*, 2021).

Low AMH levels are especially found in survivors who were treated with alkylating agents/procarbazine containing regimens, but the effect of radiotherapy on (the recovery of) AMH is less frequently described (van Beek *et al.*, 2007b; Brougham *et al.*, 2012; Decanter *et al.*, 2021). Within the papers included in this review, only a few patients were treated with radiotherapy and no additional analyses were performed. In studies on childhood cancer patient with varying diagnoses, lower AMH values were typically observed in patients receiving abdominal radiotherapy or total body irradiation (Lie Fong *et al.*, 2009; Gracia *et al.*, 2012; Miyoshi *et al.*, 2013; Elchuri *et al.*, 2016; van den Berg *et al.*, 2018; George *et al.*, 2019).

Interpretation of the results is complicated by the known decrease in AMH with age, inter-individual variation, the potential confounding

**Table V Summary of evidence on markers of reproductive ability in female and male childhood or adolescent Hodgkin lymphoma survivors.**

| Reported outcome | N studies | N HL survivors | Results |
|---|---|---|---|
| ***Females*** | **41** | **5057** | |
| Serum anti-Müllerian hormone (AMH) | 6 | 180 | *Pre-treatment*<br>• 9% of newly diagnosed HL patients had low AMH levels (<p10); 1 study; 32 patients<br>*Post-treatment*<br>• 55–59% of studied HL survivors had low AMH levels (<14 pM or <95% CI of healthy controls) after treatment, none of the studied patients had received pelvic radiotherapy; 2 studies; 46 patients<br>• A significant decrease in AMH before and after treatment was reported; 3 studies; 89 patients<br>• AMH serum levels were lower in patients treated with MOPP, when compared to patients that did not receive MOPP; 1 study; 17 patients |
| Antral follicle count (AFC) | 1 | 44 | *Post-treatment*<br>• A significant decrease in AFC before and after treatment was reported; 1 study; 13 patients |
| Premature ovarian insufficiency (POI)* | 7 | 1516 | *Post-treatment*<br>• Survivors with POI ranged from 6% to 34% (median 9%); 7 studies; 1516 patients<br>• POI was observed more often or sooner if HL treatment included (high) doses of ovarian radiotherapy; 2 studies; 912 patients |
| 'Ovarian failure' (not defined) | 3 | 154 | *Post-treatment*<br>• Ovarian failure was reported in 13–31% (median 17%); 3 studies; 154 patients<br>• Ovarian failure was observed more frequently in patients who had received pelvic radiation; 1 study; 36 patients |
| Acute ovarian failure (AOF) | 1 | 553 | *Post-treatment*<br>• 12% of the included females reported never menstruating or ceased having spontaneous menses within 5 years after cancer diagnosis; 1 study; 553 patients |
| Cycle (ir)regularity or amenorrhea | 18 | 387 | *Post-treatment*<br>• Majority of HL survivors developed or maintained regular menstrual cycles (range 79–100%, median 100%); 9 studies; 168 patients<br>• Survivors experiencing amenorrhea post-treatment ranged from 0% to 71% (median 4%); 13 studies; 240 patients<br>• Cycle irregularity was observed more frequently in patients treated with MOPP, when compared to patients that had received other chemotherapy protocols; 1 study; 16 patients<br>• 3 patients developed amenorrhea during therapy, but resumed spontaneous menses 2–4 years post-treatment; 1 study; 36 patients |
| Serum follicle stimulating hormone (FSH) | 8 | 155 | *Post-treatment*<br>• 17–100% (median 53%) of HL survivors had elevated FSH (above cutoff value 8–30 IU/l, or high in comparison to healthy controls or survivors of other types of childhood cancer); 7 studies; 132 patients<br>• A significant increase in serum FSH levels before and after treatment was reported; 1 study; 13 patients<br>• FSH serum levels were higher in patients who received pelvic radiotherapy; 4 studies; 55 patients<br>• FSH serum levels were higher in patients who received higher cumulative doses of procarbazine/MOPP; 2 studies; 44 patients<br>• In 4 patients, FSH values normalized over time, at 2–9 years post-treatment; 1 study; 14 patients |

(continued)

**Table V Continued**

| Reported outcome | N studies | N HL survivors | Results |
|---|---|---|---|
| Pregnancy or live birth | 20 | 2681 | *Post-treatment*<br>• Pregnancy or live birth was reported in 1262 out of 2388 (53%) females; 19 studies; 2388 patients<br>• A significant lower ratio of observed to expected number of live born children was reported in 110 married/cohabitant HL-surviving women, in comparison to general population, ratio 0.53: 95% CI 0.42–0.64; 1 study; 110 patients<br>• The proportion of mothers in HL survivors was comparable to a general population group, except for the age group 40–44 years old (61% of 66 HL survivors versus 78% of 2.847.000 women, $P = 0.001$); 1 study; 467 patients<br>• A negative association was seen between parenthood and pelvic radiotherapy; 1 study; 467 patients<br>• Median time to pregnancy was 42 months (3–100 months); 1 study; 26 patients<br>• There were no statistically significant differences in pregnancy outcomes observed in patients with or without ovarian transposition; 1 study; 90 patients.<br>• The number of pregnancies achieved via IUI or IVF were $n = 4/176$, $n = 2/17$, and $n = 1/10$, respectively; 3 studies; 277 patients |
| ***Males*** | **52** | **1903** | |
| Semen-analysis | 39 | 1118 | *Pre-treatment*<br>• Incidence of azoospermia in newly diagnosed HL patients ranged from 0% to 50% (median 10%); 6 studies; 109 patients<br>• Incidence of oligospermia in newly diagnosed HL patients ranged from 39% to 68% (median 55%); 3 studies; 43 patients<br>*Post-treatment*<br>• Incidence azoospermia in HL survivors ranged from 33% to 100% (median 75%); 29 studies; 332 patients<br>• Incidence oligospermia in HL survivors ranged from 0% to 33% (median 17.5%); 14 studies; 223 patients<br>• Higher incidences of abnormal sperm counts were observed in patients who had received MOPP when compared to patients receiving other chemotherapy treatments; 2 studies; 34 patients<br>• No recovery of sperm was seen in 19 HL survivors, up to 20 years post-treatment; 1 study; 19 patients<br>• 3 azoospermic and 2 oligospermic patients had late recovery (at 30, 57, 108, 18, and 19 months post-treatment, respectively); 1 study; 20 patients<br>• Semen analysis of 2 HL survivors showed late recovery (at 12 years post-treatment), the remaining 10 azoospermic boys had no recovery up to 14 years post-treatment; 1 study; 19 patients<br>• 2 azoospermic and 2 oligospermic patients had late recovery (at 14, 127, 41, and 103 months post-treatment, respectively); 1 study; 12 patients |
| Serum follicle stimulating hormone (FSH) | 28 | 738 | *Pre-treatment*<br>• Mean serum FSH values were significantly higher in HL patients, when compared to healthy controls; 1 study; 10 patients<br>*Post-treatment*<br>• Percentage of HL survivors with elevated FSH ranged from 0% to 100% (median 51.5%) (applied cutoff values ranged from >5 to >18 IU/l or >2 SD of controls); 26 studies; 672 patients<br>• Median serum FSH values were significantly higher and more often above cutoff in HL patients treated with MOPP, when compared to patients that did not receive MOPP; 2 studies; 89 patients<br>• Elevated FSH levels were observed more frequently in (post)pubertal boys, when compared to pre-pubertal boys; 2 studies; 33 patients<br>• FSH levels remained elevated up to 17 years post-treatment; 1 study; 28 patients<br>• FSH levels remained unchanged up to 8 years post-treatment; 1 study; 36 patients<br>• 1 out of 4 patients had a normalizing FSH value over time; 1 study; 4 patients<br>• In 2 patients a significant decrease in FSH value was observed over time (9–10 years post-treatment); 1 study; 20 patients |

(continued)

**Table V Continued**

| Reported outcome | N studies | N HL survivors | Results |
|---|---|---|---|
| Serum Inhibin B | 5 | 182 | *Pre-treatment*<br>• Mean serum Inhibin B values were significantly lower in HL patients, when compared to healthy controls; 1 study; 10 patients<br>*Post-treatment*<br>• Percentage of HL survivors with both elevated FSH and low inhibin B was 45–50% (median 47,5%) (applied cutoff <100 pg/ml); 2 studies; 95 patients<br>• 4 out of 21 HL survivors (19%) had low inhibin B serum levels (applied cutoff <100 pg/ml); 1 study; 21 patients<br>• Median inhibin B levels were significantly lower in patients treated with MOPP, when compared to patients that did not receive MOPP; 1 study; 56 patients |
| Serum luteinizing hormone (LH) | 24 | 604 | *Pre-treatment*<br>• Mean serum LH values were significantly higher in HL patients, when compared to healthy controls; 1 study; 10 patients<br>*Post-treatment*<br>• Percentage of HL survivors with elevated LH levels ranged from 0 to 57% (median 17%) (applied cutoff values ranged from >3 to >30 IU/l or >2 SD of controls); 21 studies; 528 patients<br>• Percentage of HL survivors with low LH levels ranged from 0 to 33% (median 0%) (applied cutoff values ranged from <0.9 up to <5 U/l); 6 studies; 75 patients<br>• Median serum LH values were significantly higher in HL patients treated with MOPP, when compared to patients that did not receive MOPP; 1 study; 56 patients<br>• Elevated LH levels were observed more frequently in late pubertal patients, when compared to pre-pubertal boys; 1 study; 15 patients<br>• Elevated LH levels were observed more frequently in patients received a more intensified chemotherapy regimen (i.e. more courses of COPP); 1 study; 65 patients.<br>• The proportion of patients who had received abdominal radiotherapy was higher among patients with elevated LH levels, when compared to patients with normal LH levels; 1 study; 49 patients.<br>• In 2 patients, LH levels were initially elevated, but returned to normal over time (6 and 11 years post-treatment). In 8 other patients, LH levels were initially within normal range, but subsequently became elevated over time (up to 12 years post-treatment); 1 study; 40 patients |
| Serum testosterone | 21 | 498 | *Pre-treatment*<br>• There were no statistically significant differences in mean serum testosterone levels of newly diagnosed HL patients and controls; 1 study; 10 patients.<br>*Post-treatment*<br>• Serum testosterone levels were within normal range; 3 studies; 79 patients<br>• There were no statistically significant differences in mean serum testosterone levels of HL survivors and controls; 1 study; 25 patients<br>• Mean testosterone levels were higher in HL survivors when compared to controls; 1 study; 45 patients<br>• There were no statistically significant differences in median serum testosterone levels of patients treated with MOPP and patients that did not receive MOPP; 1 study; 56 patients<br>• 0–43% (median 6%) of HL survivors had low testosterone serum levels (applied cutoff values ranged from <0.1 to <14 IU/l, or <2 SD of controls); 15 studies; 339 patients<br>• 0–33% (median 16,5%) of HL survivors had high testosterone serum levels (>35 nmol/l); 2 studies; 22 patients |
| Pregnancy or live birth | 13 | 755 | *Post-treatment*<br>• Pregnancy or live birth was reported in 374 out of 656 (57%) males; 13 studies; 656 patients<br>• 5 out of 24 (21%) patients with signs of germinal epithelium damage (e.g. elevated FSH levels) have children; 1 study; 24 patients<br>• None of 11 male HL survivors used their stored sperm; 1 study; 11 patients |

AFC, antral follicle count; AOF, acute ovarian failure; AMH, anti-Müllerian hormone; HL, Hodgkin lymphoma; MOPP, Mechlorethamine, Vincristine (Oncovin), Procarbazine, Prednisone; N, number; POI, premature ovarian insufficiency.

*All reports on (premature) ovarian failure before the age of 40 years, sometimes within papers referred to as non-surgical premature menopause (NSPM), were defined as POI in this review.

effect of hormonal contraceptive use, and additional variations caused by sample instability in storage, as well as variations between assays and kits (Krawczuk-Rybak et al., 2013b; Yates et al., 2019). A recent systematic review evaluated AMH as a biomarker of ovarian reserve and POI in children and women with a cancer diagnosis (Anderson et al., 2022): 11 of the included papers evaluated AMH in patients with different types of lymphoma and although not all of these studies were eligible for this review, their results were comparable to ours, as all studies reported significant declines in AMH concentrations during or after anticancer treatment (≤3 months post-treatment). Large prospective studies including pre-treatment and long-term follow-up AMH measurements are lacking, whereas the change in AMH in the individual girl or young woman may be helpful to estimate gonadotoxicity of the treatment given. This is valuable information for counseling not only female HL patients but also for HL survivors, since there may still be an opportunity to harvest oocytes in survivorship.

## Male HL survivors

In this review, high incidences of abnormal semen analyses (i.e. azoospermia, oligospermia, asthenezospermia and theratospermia) were observed in male HL survivors (post-treatment: azoospermia 33–100%; median 75%; 29 studies; 332 patients. oligospermia 0–33%; median 17.5%; 14 studies; 223 patients). Adverse effects with spermatogenesis damage were specifically present in patients treated with alkylating agents or pelvic radiotherapy, which is line with previous literature reports (Skinner et al., 2017). If spermatogenesis is impaired, FSH blood levels rise and, as expected, many studies found that males with increased FSH concentration had abnormal sperm counts (Franchimont et al., 1972; Brämswig et al., 1990; Gözdasoglu et al., 1995; Rafsanjani et al., 2007; Zaletel et al., 2010). However, a normal serum FSH does not exclude germinal epithelium damage, and azoospermia was also reported in boys with normal endocrine markers (de Kretser et al., 1974; Green and Hall, 1988; Brämswig et al., 1990; Kader and Rostom, 1991; Chan et al., 2001; Bordallo et al., 2004; Hobbie et al. 2005). It is thought that the detection of serum inhibin B, in the presence of FSH (inhibin B/FSH ratio), is the best indirect marker of male infertility (Bordallo et al., 2004; van Casteren et al., 2008). Unfortunately, inhibin B serum concentrations were not often included as an outcome measurement in the studies included in this review. Only four studies reported on inhibin B serum concentrations after treatment, and one specifically evaluated the inhibin B/FSH ratio (van Beek et al., 2007a; Bordallo et al., 2004; Brignardello et al., 2016; Felicetti et al., 2020). In general, inhibin B levels appeared to be lower in the HL group when compared to healthy controls and a significant association was observed with sperm quality (Bordallo et al., 2004).

The value of LH and testosterone as serum markers of reproductive ability remains debatable (Krawczuk et al., 2012; Keskin et al., 2015). Primarily, the rapidly dividing stem cells and Sertoli cells are affected by irradiation and cytostatic agents, and often Leydig cells appear to be spared. Most male childhood cancer survivors undergo normal pubertal development with normal testosterone concentrations, and androgen replacement therapy in cancer survivors is rare (Stukenborg et al., 2018b). Within this review, LH and testosterone levels were indeed less evidently affected when compared to FSH levels (median percentage of patients with elevated LH 17%, low testosterone 6%, elevated FSH 51.5%). Still, boys with decreased testosterone values during puberty may be at risk of delayed sexual maturation, although such cases are almost exclusively described in boys with testicular cancer or those receiving extremely high doses of pelvic radiation (or non-malignant disorders) (Sklar et al., 1990; Amano et al., 2013; Goossens et al., 2020).

Studies presented varying results on recovery of reproductive ability in male HL survivors during follow-up (da Cunha et al., 1984; Green and Hall, 1988; Anselmo et al., 1990; Ortin et al., 1990; Heikens et al. 1996; Bordallo et al., 2004). In most patients, serum markers remained abnormal, although only a limited number of patients underwent sequential sampling for a long period of time. Recovery of semen quality is usually reported within the first months after treatment but can also occur years after treatment completion. For example, late recovery was established in survivors with (initially) azoospermia at 114 months post-treatment or even 12 years after treatment (da Cunha et al., 1984; Ortin et al, 1990). Although recovery of sperm appears to be correlated with the cumulative total dose of chemotherapy and pelvic radiotherapy, it is very difficult to predict whether spermatogenesis will normalize after treatment, and full recovery does not appear to occur often (Sherins et al., 1978; Bonadonna, 1982; da Cunha et al., 1984; Naysmith et al., 1998). For some male cancer survivors, testicular sperm extraction followed by ICSI can help in achieving biologic fatherhood but, generally, the therapeutic options are limited and prognosis is poor in case of severely damaged gonads (Meseguer et al., 2003; Hsiao et al., 2011). Therefore, it is highly recommended to offer pre-treatment sperm banking to all boys who are able to produce semen physically, but this would also be based on emotional and cognitive status (Wallace, 2011; Loren et al., 2013). In previous studies including young boys diagnosed with HL, the youngest patient with an ejaculate containing motile spermatozoa was 12.2 years old, and the smallest testicular volumes were 6–7 ml (Bahadur et al., 2002; Hagenäs et al., 2010; Daudin et al., 2015; Adam et al., 2020). For young, pre-pubertal boys at high risk of infertility, a testicular tissue biopsy for cryopreservation could be considered (Goossens et al., 2020; Mulder et al., 2021a).

## Treatment-related factors

In both sexes, adverse effects were specifically present in treatment protocols using alkylating chemotherapy agents, a higher cumulative dose of chemotherapy, a large number of treatment cycles, and/or infra-diaphragmic radiotherapy (Whitehead et al., 1982; da Cunha et al., 1984; Anselmo et al., 1990; Brämswig et al., 1990; Bokemeyer et al., 1994; Ben Arush et al., 2000; van Beek et al., 2007a; 2007b; Aubier et al., 1989; van der Kaaij et al., 2012b; Brignardello et al., 2016). Patients also appeared to be at increased risk of disturbed spermatogenesis after HSCT, probably linked to the use of radiotherapy and high doses of alkylating treatment in the myeloablative treatment pre-HSCT (Brignardello et al., 2016; Laddaga et al., 2022). To ensure the highest survival rates with the least adverse effects, treatment protocols for childhood HL are constantly being evaluated and adapted. Over the past decades, many chemotherapy regimens have been used for HL treatment, all with (slightly) different working mechanisms, and differing gonadal toxicity as well. The ABVD regimen was shown to be as effective as the classical MOPP regimen, but less damaging for gonadal function (Bonadonna et al., 1984, 1989; Viviani et al., 1985; Canellos et al., 1992). Some of the included studies compared

ABVD to the MOPP regimen and confirmed this statement: ABVD resulted in less azoospermia and there was no statistically significant decrease in AMH serum levels after treatment with ABVD, while the MOPP regimen was associated with a significantly lower AMH post-treatment (Anselmo *et al.*, 1990; Dhabhar *et al.*, 1993; Berjeb *et al.*, 2020). Another study used ~50% less cyclophosphamide and procarbazine in their C-MOPP/ABV treatment protocol but still found severe damage to germinal epithelium (Bordallo *et al.*, 2004). These results suggest that even a small dosage of alkylating agents may be gonadotoxic in males. Efforts should be made to avoid or minimize the potential risk of drug-induced gonadal failure by avoiding the use of alkylating agents if possible.

Recently, robust evidence for the beneficial effects of replacing procarbazine with dacarbazine on gonadotoxicity was provided by the (randomized) Euronet-PHL-C1 study (Mauz-Körholz *et al.*, 2022): the paper was published after completion of our literature search, therefore these findings were not included in the results section of this review. Male patients receiving COPP (Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisone) treatment (with procarbazine) more often had azoospermia, significantly higher FSH serum levels, and lower inhibin B concentrations when compared to patients receiving COPDAC (with dacarbazine). The 5-year event-free survival rates of both treatment arms were within the same range (around 90%). The Euronet-PHL-C1 study also revealed that radiotherapy could safely be omitted in patients who responded adequately to treatment, which further contributes to the reduction of treatment-related gonadotoxicity.

The current Euronet-PHL-C2 study is evaluating whether radiotherapy can be reduced even more, by intensifying chemotherapy with higher doses of cyclophosphamide (Clinical trials; NCT02684708). The effects of the C2 treatment protocol on reproductive potential are being studied in detail within the ongoing fertility add-on study. Moreover, several other newly introduced drugs are considered to be non-gonadotoxic, such as Brentuximab, Nivolumab and Pembrolizumab, but studies still need to confirm their safety and effectivity.

## Effect of HL

In addition to the adverse effects of treatment for HL on fertility, there might also be a negative effect of the disease itself. In a study that compared pre-treatment semen analyses of males with different cancer types, semen parameters were particularly affected in HL patients and testicular tumors, in comparison to patients with other types of cancer and controls (Caponecchia *et al.*, 2016). Within this review, we noticed that abnormalities in semen analysis were often present before anticancer treatment was administered (pre-treatment analyses: 0–50% azoospermia; median 7.5%; six studies; 109 patients, 39–68% oligospermia; median 54.5%; three studies; 43 patients). Based on studies in adult HL patients, the higher metabolic and inflammatory state in HL patients appears to affect semen quality negatively (Botchan *et al.*, 1997; Hallak *et al.*, 2000; Agarwal and Allamaneni, 2005; Trottmann *et al.*, 2007; van der Kaaij *et al.*, 2009). Pre-treatment azoospermia is mostly seen in patients with B-symptoms (weight loss, fever and drenching night sweats), which might in part be related to the well-known adverse effect of elevated scrotal temperature on spermatogenesis (Carlsen *et al.*, 2003; van der Kaaij *et al.*, 2009; Caponecchia *et al.*, 2016). A study in pediatric HL patients revealed that not only sperm counts but also serum inhibin B concentrations were significantly lower in patients with B-symptoms, when compared to patients presenting without B-symptoms ($P = 0.05$ and $P < 0.05$, respectively) (van Beek *et al.*, 2007a).

One of the studies included in this review, demonstrated that not all patients with abnormal semen at time of diagnosis had abnormal semen quality after treatment (n = 4/8, 50%) (Laddaga *et al.*, 2022). Hypothetically, disease activity may temporarily affect spermatogenesis, but it remains highly complex to analyze a potential association of HL itself with semen quality after treatment, because of the confounding effects of treatment.

Moreover, the study by van Dorp *et al.* reported decreased AMH levels in their pre-treatment analyses in girls with newly diagnosed lymphoma, which may also be explained by the high cytokine expression associated with HL (van Dorp *et al.*, 2014; Paradisi *et al.*, 2016). One of the included studies assessed the presence of B-symptoms as a risk factor of having POI after treatment and observed no statistically significant correlation (van der Kaaij *et al.*, 2012b). Additional exploration of the hypothesized pathophysiological pathways would be appropriate, as a compromised reproductive function before the start of chemotherapy would affect the chance of successful fertility preservation.

## Age at diagnosis

Pennisi *et al.* (1975) suggested that chemotherapy-induced gonadal damage is related to the age of the cancer patient at treatment, with young age being a relative protecting factor. In their small study, they treated 23 boys and 11 girls with nephrosis with cyclophosphamide, and almost exclusively found abnormal spermatogenesis and increased FSH levels in post-pubertal boys. It was thought that the epithelium of the seminiferous tubules is relatively dormant before puberty and thereby less sensitive to cytotoxic agents (Sherins *et al.*, 1978; Bayle-Weisgerber *et al.*, 1984). Likewise, Brämswig *et al.* (1990) found a correlation between a lower quality of semen and being post-pubertal at treatment. Another study reported a significantly lower probability of developing POI for NHL and HL survivors below the age of 25 years, compared with those over 25 years ($P < 0.03$) (Bokemeyer *et al.*, 1994). Nevertheless, multiple additional studies did not find such a correlation of age at treatment with chemotherapy-induced gonadotoxicity (Shafford *et al.*, 1993; Mackie *et al.*, 1996; Ben Arush *et al.*, 2000; Hobbie *et al.*, 2005; van Beek *et al.*, 2007b; Aubier *et al.*, 1989; Romerius *et al.*, 2010; Zaletel *et al.*, 2010; van der Kaaij *et al.*, 2012b; Brignardello *et al.*, 2016). In most studies the number of patients is limited, which affects the reliability of sensitivity analyses, and the results may well be affected by other patient- or treatment-related characteristics.

## Chance to conceive

Based on the included reports on parenthood, having children as a HL survivor is certainly not impossible. Yet, it remains very complex to evaluate data on fertility-related outcomes and to define the chance to achieve pregnancy in HL survivors. There are many factors that affect fertility (e.g. age, BMI, alcohol and drug use, menstrual cycle, additional medical history, fertility potential of the partner), but these are often poorly documented in papers presenting pregnancy outcomes in cancer survivors. In most of the included studies, results were restricted

to the number of patients obtaining a pregnancy or live birth, while it would be appropriate to also mention the percentage of females wishing to have (more) children but failing to succeed. Nonetheless, pregnancy cases were documented in male survivors with 'abnormal' fertility markers, such as high FSH values or (severe) oligospermia, which demonstrates that the presence of aberrant markers of fertility does not explicitly exclude the chance to conceive (Chapman et al., 1979; Waxman et al., 1982; Kreuser et al., 1987; van den Berg et al., 2004; Bordallo et al., 2004; van Casteren et al., 2008). Similarly, females with low AMH may still have a chance to become pregnant, as long as they have an ovulatory cycle, as a low oocyte quantity does not define the quality of the follicles (di Paola et al., 2013). Nevertheless, reproductive treatment may help males and females with a history of cancer treatment to extend their reproductive lifespan and chance of pregnancy. Therefore, personalized fertility counseling is strongly recommended.

## Strengths and limitations

This review is the first complete overview of the literature on pre-existing and treatment-related gonadotoxicity in both male and female childhood HL survivors.

The present review is a narrative review. Owing to the lack of standardized evaluation of reproductive potential among HL survivors, the available evidence on fertility after HL treatment is heterogenous and it is difficult to compare or combine results. Only a few eligible studies included control or reference groups. Therefore, the results presented remain descriptive and meta-analyses could not be performed, while stratified analyses would have been favored to analyze the effect of treatment- or diagnosis-related factors (such as age at diagnosis or treatment protocol applied) on reproductive potential. Quality of studies was not assessed systematically within this review, as the overall level of evidence was poor and a time-consuming appraisal of each study would not have provided useful information. If future studies on fertility after cancer treatment are performed in a more structured way, a systematic review with critical appraisal could be conducted, in order to achieve a higher level of evidence. Nonetheless, the current review gives an overview of best available evidence of a clinically relevant topic, useful for both HL survivors and the clinicians treating them in terms of potential late effects.

Still, several comments on quality of included studies should be made. Most studies were performed in small groups of childhood HL survivors, or in cohorts with multiple types of childhood cancer survivors with only a few HL survivors included. Studies did not always include a control group, or the comparison groups were small or based on another group of cancer patients. Many studies on menstrual cycle and pregnancy outcomes used questionnaires to collect results, which increases risk of bias and imprecision. The included trials were published between 1978 and 2021, and the older studies in females may not have assessed AMH as a reproductive marker, as it can be considered a relatively new approach. Moreover, poor methodology for semen analysis due to minimal standardization at the time of older studies may have affected the results. In 2015, a checklist for author and reviewers was published to help ensure that an appropriate and robust methodology of semen analysis is carried out, which may contribute to more reliable results on semen quality in the future (Björndahl et al., 2016). Nevertheless, for male cancer survivors, mainly azoospermia is of clinical relevance and we expect less uncertainty in semen analysis reporting a zero sperm count.

In general, the young age of cancer patients may complicate the evaluation of some markers of reproductive function. Young boys may be physically or cognitively unable to produce semen and AFC measurement in girls may be disregarded owing to the invasive measurement via transvaginal ultrasound.

Many studies were cross-sectional, meaning that they only performed one measurement at a single time point. Gonadotoxic effects may become clearer after time passes by, and to evaluate potential recovery multiple assessments are crucial to provide valid results. Studies assessing POI require a minimal follow-up of the entire study population after the age of 40 years old, but a long follow-up period is highly recommended for all studies in female or male HL survivors.

Over the past years, treatment for HL has improved and some of applied treatment protocols are not commonly used anymore. Since the severe gonadotoxicity of alkylating agents was pointed out, treatment regimens have been adjusted, and the dosage of alkylating drugs and radiation are reduced, or replaced if possible (Mauz-Körholz et al., 2010, 2022). The results of the studies included in this review may be mainly valuable for survivors who have been treated with these particular regimens and less relevant for patients who are currently undergoing treatment.

## Implications for further research and daily practice

The effects of HL and (current) treatment regimens on reproductive ability should be studied more intensely. We recommend focusing on longitudinal prospective studies with repeated measurements (for example before and during treatment, up to yearly during the first few years after treatment, with subsequent longer time-intervals during follow-up) and a combination of reproductive markers (such as semen analysis, FSH and inhibin B in males, and AMH, AFC and FSH in females). We highly encourage future researchers to further analyze the effect of specific treatment- and diagnosis-related factors on direct and indirect adverse effects as well as (failure of) recovery over time. We suggest analyzing the commonly assessed parameters such as abdominal radiotherapy (yes/no), CED score (cyclophosphamide equivalent dose, using the cutoff $>6000\,mg/m^2$ in girls and $>4000\,mg/m^2$ in boys in line with the PANCARE guidelines (Mulder et al., 2021a,b)), and age at diagnosis (pre-/post-pubertal), but trials should, above all, aim to study the effects of more unknown agents (e.g. dacarbazine) and newly introduced drugs that are thought to be non-gonadotoxic (e.g. Brentuximab, Nivolumab and Pembrolizumab).

With these data, clinical guideline for fertility preservation in future HL patients can be updated, and patients at risk of impaired gonadal function or a reduced fertility lifespan can be better informed on the methods available to preserve fertility and timing of parenthood (Mulder et al., 2021a,b). Until then, (future) fertility and the possibility of fertility preservation (e.g. storage of semen or harvesting testicular tissue for boys, and oocyte or ovarian tissue cryopreservation in girls) should always be considered when treating (young) cancer patients (Wallace, 2011; Loren et al., 2013; Goossens et al., 2020; Mulder et al., 2021a,b; van der Perk et al., 2021).

## Conclusion

HL treatment, primarily when high doses of chemotherapy, alkylating agents and/or pelvic radiotherapy are administered, can negatively affect reproductive ability in both female and male survivors. Problems with fertility can seriously affect psychological wellbeing and quality of life, and patients at risk of impaired gonadal function or a shortened reproductive lifespan should be well informed on the methods available to preserve fertility and the timing of parenthood.

Treatment regimens for HL rapidly evolve to ensure the highest survival rates with the least adverse effects.

Studies on fertility after HL treatment are heterogeneous owing to the lack of structured evaluation of markers of reproductive potential. The overall quality of evidence is poor and additional studies on markers of reproductive function in cancer survivors are needed. We recommend the use of repeated measurements and a combination of reproductive markers next to clinical outcomes to continuously study the effects of HL and (current) treatment regimens on reproductive capacity.

## Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

## Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

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## Authors' roles

K.C.E.D., M.C.F.P., F.S., S.M., E.v.D.-d.B., M.A.V., and S.L.B. participated in the design of the paper. L.J.S. contributed to the search. K.C.E.D., M.C.F.P., S.M., E.v.D.-d.B., and M.A.V. screened for eligible articles and K.C.E.D. and M.C.F.P. extracted data. K.C.E.D. analyzed the data and drafted the first version of the manuscript. All authors were involved in the data interpretation, contributed to the manuscript writing and approved the final version.

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## Conflict of interest

The authors are involved in the ongoing fertility add-on study, nested within the EuroNet-PHL-C2 study (Clinicaltrials NCT02684708; EudraCT number 2012-004053-88). This study evaluates gonadal function and fertility in children treated according to the EuroNet-PHL-C2 protocol.

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