Gonadal Function and Fertility in Survivors After Hodgkin Lymphoma Treatment Within the German Hodgkin Study Group HD13 to HD15 Trials

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ABSTRACT

Purpose
To optimize fertility advice in patients with Hodgkin lymphoma (HL) before therapy and during survivorship, information on the impact of chemotherapy is needed. Therefore, we analyzed gonadal functions in survivors of HL.

Patients and Methods
Women younger than age 40 and men younger than 50 years at diagnosis in ongoing remission at least 1 year after therapy within the German Hodgkin Study Group HD13 to HD15 trials for early- and advanced-stage HL were included. Hormone parameters, menstrual cycle, symptoms of hypogonadism, and offspring were evaluated.

Results
A total of 1,323 (55%) of 2,412 contacted female and male survivors were evaluable for the current analysis (mean follow-up, 46 and 48 months, respectively). Follicle-stimulating hormone, anti-Müllerian hormone, and inhibin B levels correlated significantly with therapy intensity (P < .001). Low birth rates were observed in survivors after advanced-stage treatment within the observation time (women, 6.5%; men, 3.3%). Regular menstrual cycle was reported by more than 90% of women younger than age 40 and men younger than 50 years at diagnosis in ongoing remission and advanced-stage HL (recovery time mostly ≤ 12 months). After six to eight cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, menstrual activity was strongly related to age (< vs ≥ 30 years: 82% vs 45%, respectively; P < .001; prolonged recovery time). Thirty-four percent of women age ≥ 30 years suffered severe menopausal symptoms (three- to four-fold more frequently than expected). In contrast, male survivors had mean levels of testosterone within the normal range and reported no increased symptoms of hypogonadism.

Conclusion
The present analysis in a large group of survivors of HL provides well-grounded information on gonadal toxicity of currently used treatment regimens and allows risk-adapted fertility preservation and comprehensive support during therapy and follow-up.

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INTRODUCTION

High overall survival rates (approximately 90%) in early- and advanced-stage Hodgkin lymphoma (HL) have been achieved.1-3 Thus, current clinical research focuses on the short- and long-term sequelae in the growing number of young survivors of HL. Among these sequelae, infertility and hypogonadism are of particular importance for patients and survivors and demand specialized medical care.4-8

Health care professionals need comprehensive information on treatment-related gonadal toxicity. At diagnosis, physicians should inform the patient thoroughly and consider protective methods to preserve fertility in time. During the follow-up period, survivors need professional advice when they desire to have children. Furthermore, it is essential to detect and maybe to treat symptoms of hypogonadism. Unfortunately, these issues are still not routinely addressed by most physicians.5,9

It is known that the rate of treatment-induced infertility increases with more aggressive chemotherapy.10-14 However, there still are many open questions about the probability of amenorrhea, reduced ovarian reserve, and infertility after distinct chemotherapies and the impact of age at treatment onset, as
well as about the chance of recovery and the risk of suffering from symptoms of hypogonadism. Thus, more detailed information is needed for both patients and physicians. Therefore, the main objective of the present analysis is to provide data on the impact of currently used chemotherapy in HL on gonadal function.

**PATIENTS AND METHODS**

**HD13 to HD15 Trials: Patients and Study Design**

Patients (age 18 to 75 years) with biopsy-proven HL were included in trials for early favorable (HD13, two cycles of doxorubicin, vinblastine, and dacarbazine with bleomycin [ABVD] or without bleomycin), early unfavorable (HD14, arm A: four cycles of ABVD or arm B: two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP] followed by two cycles of ABVD [2+2]), or advanced-stage HL (HD15, six to eight cycles of escalated BEACOPP or eight cycles of BEACOPP-14).1-3 The studies were carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Assessment of Gonadal Function and Fertility

All survivors (age at random assignment: women, 18 to 39 years; men, 18 to 49 years) in ongoing remission at least 1 year after therapy and without any other treatment than the HD13 to HD15 trial medication were addressed. In women, results were stratified with respect to age (cutoff, 30 years).12,15 In men, we interpreted inhibin B in the context of follicle-stimulating hormone (FSH) levels to achieve the highest positive predictive value with a cutoff for the inhibin B/FSH ratio corresponding to proven fertile men and cutoff levels for FSH and inhibin B corresponding to oligospermia.16,17

**Questionnaires**

Symptoms of hypogonadism were determined using the Menopause Rating Scale (MRS) and the Aging Males’ Symptoms scale.18-21 Additional questions referred to the use of hormonal substitution, methods of fertility preservation before therapy, menstrual status, pregnancies and offspring after normal and in vitro fertilization, and social aspects.

**Hormone Analysis**

Survivors were asked to take a blood sample (samples for women were taken on day 3 of a new menstrual cycle or at the end of the pill break). Blood samples were then centrally processed and stored at −80°C until analysis. Tests included standardized assays for FSH, lutheinizing hormone (LH), estradiol, and testosterone (heterogenic, noncompetitive chemiluminscent immunometric assays; Elecsys-FSH, Elecsys-LH, Elecsys-Estradiol-II, Elecsys-Testosterone-II; Roche Diagnostics, Mannheim, Germany); anti-Müllerian hormone (AMH; active AMH Gen-II ELISA; Beckman Coulter, Prague, Czech Republic); and inhibin B (inhibin B Gen-II ELISA-KIT; Beckman Coulter).

**Statistics**

In female survivors (≤40 years old at first diagnosis of HL and ≤45 years old at time of fertility assessment), results are reported in age groups (18 to 29 years and 30 to 45 years). For men, the upper age limit at time of fertility assessment was 57 years. Outcome measures of female fertility were menstrual activity, time to resumption of menstrual activity, hormone values, MRS, offspring, and pregnancies after therapy. Hormone levels were natural log-transformed before statistical computations to normalize distributions. Fertility parameters in HD15 survivors are additionally stratified for the use of gonadotropin-releasing hormone (GnRH) analogs. Results are presented with descriptive statistics and 95% CIs. To provide a more detailed analysis of age effects in female survivors, we computed a logistic regression of amenorrhea (562 women and 761 men; Fig 1). In women and men, mean age at fertility assessment was 32 and 38 years, respectively, and mean observation time from the end of treatment was 46 and 48 months, respectively. Comparing all trials, there were unfavorable conditions for patients treated in the HD13 trial, with higher age at fertility assessment (women, 36 years; men, 40 years) and a higher proportion of patients having children before therapy (women, 47%; men, 57%). There were balanced conditions for patients treated in the HD14 and HD15 trials (Table 1). Comparison of the participating and nonparticipating patients qualifying for our analysis showed no relevant differences (Appendix Table A1, online only).

**Female Survivors**

**Hormones in female survivors.** Differences in favor of early-stage patients treated with fewer cycles (two to four instead of six to eight cycles) of less intensive chemotherapy were high and significant for AMH and FSH in both age groups (P < .001). Hormone levels were

![Fig 1. CONSORT diagram.](image-url)
different with respect to age; mean AMH levels greater than 2 μg/L were only observed in women younger than 30 years after ABVD therapy (Table 2). After HD15 therapy, mean AMH levels were 0 μg/L in both age groups, and the highest FSH levels were measured (mean FSH: < 30 years, 11.1 U/L; ≥ 30 years, 29.7 U/L). Serum levels of AMH and FSH differed between treatment groups in the HD14 trial. These differences in favor of ABVD were high and significant for FSH in older women (mean FSH in women age 30 to 45 years: arm A, 4.4 U/L; arm B, 11.8 U/L; arm C, 11.1 U/L; arm D, 11.8 U/L; P < .001) and for AMH in both age groups (mean AMH in women age < 30 years: arm A, 2.3 μg/L; arm B, 0.9 μg/L; arm C, 0.7 μg/L; arm D, 0.3 μg/L; P < .001). In contrast, no difference was found between the three BEACOPP arms of the HD15 trial (P > .15).

Regular cycle and time to resumption of menstrual activity. In both age groups, more than 90% of survivors after treatment for early-stage HL reported a regular cycle after therapy, and time to resumption of menstrual activity was mostly reached within 1 year (Fig 2A). After treatment for advanced-stage HL, 82% of women younger than 30 years had a regular cycle, compared with only 45% of women in the older age group (Table 2). There was no difference regarding whether or not women had received cotreatment with GnRH analogs. Time to resumption of menstrual activity took considerably longer than in early-stage patients and was strongly related to age (Fig 2A). The mean age of women with sustained amenorrhea (95% CI, 30.5 to 32.8 years), whereas the mean age of women with a regular cycle was 27.1 years.
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Abbreviations: A(B)VD, doxorubicin, (bleomycin), vinblastine, and dacarbazine; AMH, anti-Müllerian hormone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; MRS, Menopause Rating Scale; 2+2, two cycles of BEACOPP followed by two cycles of ABVD.

*Total No. represents number of patients with valid data, and percentages represent percentages of patients with valid data.
†Survivors of the HD15 study grouped according to (nonrandomized) treatment with GnRH.
‡All computations for AMH and FSH are log-transformed values to normalize distributions; table entries are in original units (after exponentiation).
§Sensitivity analysis in a subgroup of survivors who did not take oral contraceptives/hormone replacement therapy.
¶Classification of MRS total score with reference scores for 45- to 60-year-old German women in parentheses.
Pregnancies and Offspring

In contrast to women after treatment for early-stage HL, fewer pregnancies were reported in women after treatment for advanced-stage HL (HD13 + HD14, n = 60, 19%; HD15, n = 22, 10%; Table 2). After HD15 therapy, 51.9% of female survivors reported a desire to have children, but only 15% reported parenthood at 4 years. In advanced-stage patients, GnRH analogs had no influence on pregnancies after therapy in contrast to observed results after treatment for early unfavorable HL.22

Menopausal symptoms. MRS total score showed no significant difference between HL trials regarding menopausal symptoms in women ≤ 30 years. An age-related increase of severe menopausal symptoms was observed in all trials. Severe symptoms were four- to five-fold more frequent in women ≥ 30 years after therapy for advanced-stage HL compared with a 45- to 60-year-old German reference cohort (Table 2). MRS correlated significantly with menstrual activity (P < .001), as well as with LH and FSH levels (P < .001). Only 48.9% of women with severe symptoms were on hormone medication at the time of the survey.

Male Survivors

Hormones in male survivors. Serum levels of inhibin B and FSH were significantly different between trials in favor of early-stage patients treated with fewer cycles (two to four instead of six to eight cycles) of less intensive chemotherapy (P < .001). Importantly, in the HD14 trial, FSH and inhibin B values differed significantly between treatment arms in favor of ABVD. No difference was found between the three BEACOPP regimens in HD15 (Table 3).

With few exceptions, inhibin B and FSH levels corresponding to proven fertility (inhibin B/FSH ratio > 23.5 ng/U) were only seen after ABVD or 2 + 2 (HD13, 51.2%; HD14, 50.4%; HD15, 0.5%). The highest proportions of inhibin B and FSH levels corresponding to oligospermia (inhibin B < 80 ng/L and FSH > 10 U/L) were measured after BEACOPP (HD13, 12.2%; HD14, 20.7%; HD15, 88.8%; Fig 3A). LH levels increased significantly with disease stage (highest mean value of 7.3 U/L after HD15 treatment; normal range, 1.7 to 8.6 U/L). Mean testosterone levels were within the normal range of 2.8 to 8.0 ng/L after all treatment regimens (Table 3).

Effect of follow-up time and age on inhibin B and FSH levels. A significant effect of follow-up time on inhibin B and FSH levels, indicating a recovery of spermatogenesis, was found after treatment with the 2 + 2 regimen (P < .001). Overall, in the HD14 trial, these hormone levels differed significantly in favor of four cycles of ABVD (P < .001); however, the subgroup of survivors with a follow-up of ≥ 4 years showed similar hormone levels in both treatment groups (Fig 4). No recovery was found in survivors of advanced-stage HL. There was an effect of age in all three trials, with favorable hormone levels in younger survivors (HD13: P = .08; HD14: P < .001; HD15: P < .001; data not shown).

Effect of age on testosterone. In survivors after HD14 and HD15 treatment, a significant age effect was found, with higher testosterone levels in younger men (HD14: P = .002; HD15: P < .001). In a multivariate analysis adjusting for the effect of study, age remained an independent predictor of testosterone value (data not shown).

Utilization of cryopreserved sperm, birth rate, and children after therapy. The birth rate after treatment in the HD15 trial was significantly lower compared with after treatment for early stages (study comparison: P = .04). Children after natural fertilization were most frequently reported in survivors after early-stage therapy compared with advanced-stage therapy (22 v two children, respectively, in HD15; Fig 3B). Two hundred seventy-four male survivors (38%) underwent a cryopreservation of sperm before therapy (Table 1). The proportion was highest (71%) in 18- to 29-year-old men. Twenty-six of these survivors (10%) used their cryopreserved sperm for assisted reproduction (21 survivors of advanced-stage HL). Thirty-two percent of male survivors after HD15 therapy reported desire for children, but only 12% reported parenthood at a median follow-up time of 4 years.

Aging Males’ Symptoms scale. Aging male symptoms were not different between patients in the trials and reference values (Table 3). No correlation between symptoms and hormonal levels, especially testosterone, was found.
DISCUSSION

With a total of 1,323 survivors of HL treated within the German Hodgkin Study Group HD13 to HD15 trials, to our knowledge, this is the largest detailed study on gonadal function and fertility after chemotherapy reported so far. The following major findings emerge from this analysis:

First, as expected, hormone levels correlate with the intensity of chemotherapy. In women, age was also a relevant factor for a reduced ovarian reserve. Normal mean AMH levels (≥ 2 µg/L) were observed in women younger than 30 years after two to four cycles of ABVD early-stage treatment, but AMH levels were compromised in survivors ≥ 30 years old. After treatment with six to eight cycles of BEACOPP, mean AMH levels were 0 µg/L in both age groups, and the highest FSH levels were measured in women older than 30 years.

In men, half of the survivors after early-stage treatment had FSH and inhibin B levels corresponding to proven fertile men, whereas...
88.8% of survivors after advanced-stage treatment had levels corresponding to oligospermia. An effect of follow-up time on inhibin B and FSH levels was found in men after 2+/H110012 treatment, suggesting a recovery up to 4 years after intermediate aggressive therapies. In contrast to the dose-dependent effect on the spermatogenesis as indicated by FSH and inhibin B, mean testosterone levels were within the normal range also after eight cycles of escalated BEACOPP.

Second, recovery of regular cycle was reported by more than 90% of women after early-stage treatment and was mostly completed within 1 year. In contrast, after treatment for advanced-stage HL, age at therapy onset was a decisive factor, and time to resumption of menstrual activity was considerably longer.

Third, compared with survivors after early-stage therapy, lower birth rates were observed in survivors after advanced-stage therapy (women: 15% vs 6.5%, respectively; men: 7.2% vs 3.3%, respectively). Of 52% of women and 32% of men with desire for children, only 15% and 12% reported parenthood within a median observation time of 4 years after advanced-stage therapy, respectively. Finally, female survivors older than age 30 years at diagnosis suffered three- to four-fold more frequently from severe menopausal symptoms compared with a 45- to 60-year-old German reference cohort.

The present analysis combines information from hormonal analyses with clinical data from large controlled trials and data obtained from standardized self-reported questionnaires. A portion of survivors did not respond, which might cause a bias. However, all information from our original trials indicated no major differences between participants and nonparticipants (Appendix Table A1). Also, comparable participation rates in all trials indicate a high external validity.

As expected, chemotherapy-induced gonadal toxicity was highest after six to eight cycles of escalated BEACOPP (-14) in both female and male survivors of HL. After this regimen, hormonal levels reflect reduced ovarian reserve and amenorrhea indicates impaired fertility in the majority of women, and a relevant impairment of spermatogenesis occurred in the majority of men. However, in advanced-stage HL, aggressive therapy results in the highest overall survival rates reported.
in large prospective trials.1-3 Thus, balancing efficacy and toxicity is a difficult task for both patients and physicians. The detailed information from our analysis might contribute to a well-balanced shared decision-making process.

In women with cancer, AMH has been investigated as a presumably valuable cycle-independent marker of the ovarian reserve.23-30 In our analysis, AMH levels were significantly worse after more intensive alkylating agent–containing chemotherapy and with older age. This was also true for FSH values; however, FSH showed a better differentiation between the group of women with a regular cycle and the group suffering from amenorrhea after therapy. Additionally, in women younger than 30 years after advanced-stage HL, the mean AMH level was 0 μg/L. However, we observed pregnancies in women with low or even undetectable AMH levels, as previously reported in women without history of cancer.21,32 These findings underline the need to further analyze the relevance of AMH assessment in female survivors of cancer. AMH is obviously not suited to predict fertility in individual patients. However, low AMH levels might indicate a reduced ovarian reserve and thus an increased risk of future premature ovarian failure. This risk cannot be estimated from our study because of the limited observation time.33

In addition, chemotherapy-induced amenorrhea might indicate infertility.12 After advanced-stage treatment, age ≥ 30 years at diagnosis had the strongest impact on the risk of sustained amenorrhea 4 years after therapy. Surprisingly, in women younger than age 30 years, a high proportion (82%) reported a regular cycle despite escalated BEACOPP chemotherapy. Nonetheless, overall, women face a relevant risk of infertility after BEACOPP chemotherapy. The protective effects of GnRH analogs observed after intermediate aggressive therapies (four cycles of ABVD or 2 + 2),22 however, could not be documented after BEACOPP therapy for advanced-stage HL in this analysis. Finally, in the cohort of women ≥ 30 years old at diagnosis, we found a surprisingly high proportion of women with severe menopausal symptoms.18 Again, age itself had a stronger negative impact on menopausal symptoms than treatment intensity. Interestingly, only 48.9% of women with severe symptoms were on hormone medication at the time of the survey. Because menopausal symptoms often substantially affect women’s quality of life and might be easy to ameliorate with hormonal replacement therapy, this finding definitively needs further investigation.

In male survivors, we found a high proportion (88.8%) of oligospermia, indicated by FSH and inhibin B levels, after six to eight cycles of BEACOPP. Even only two cycles of escalated BEACOPP in the 2 + 2 regimen induced a marked decrease in the proportion of patients having hormone levels corresponding to proven fertile men (25%) compared with four cycles of ABVD (50%). This finding underscores the lower gonadoxic potential of the ABVD regimen.35,36 Only 30% of male survivors after advanced-stage therapy reported desire for children at 4 years. This observation time might be too short to finally judge on paternity, which was documented in only 12 men (two after natural fertilization and 10 after assisted reproduction). Thus, to maintain the chance for assisted reproduction, cryopreservation of sperm or testicular sperm extraction must be offered before starting aggressive therapy.37 Interestingly, levels of testosterone were also within the normal range after escalated BEACOPP therapy, supporting the hypothesis that Leydig cells are more resistant to cytotoxic chemotherapy.11,34,38,39 Also, mean aging male symptoms were within the normal range in our analysis.

To summarize, survivors after BEACOPP treatment for advanced-stage disease have the highest risk for symptomatic gonadal dysfunction. However, data directly comparing six to eight cycles ABVD to six to eight cycles of escalated BEACOPP in patients with HL should be generated to exactly quantify risk of treatment options in the context of gonadal toxicity. Until then, the information derived from our analysis may improve both the shared decision-making process regarding individual treatment decisions and the guidance during survivorship.

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