

Gonadal Function Recovery in Patients With Advanced Hodgkin Lymphoma Treated With a PET-Adapted Regimen: Prospective Analysis of a Randomized Phase III Trial (AHL2011)

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abstract

PURPOSE The prospective, randomized AHL2011 trial demonstrated that the use of the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen (ABVD) after two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP_{escalated}) in early responders on the basis of a positron emission tomography (PET)–driven strategy was safe and minimized toxicity compared with standard 6 BEACOPP_{escalated} cycles. This substudy investigated the benefit of this strategy in gonadal function and fertility in patients under 45 years old.

METHODS Ovarian function was assessed by serum measurement of follicle-stimulating hormone (FSH), estradiol, and anti-müllerian hormone in women, and semen analysis, FSH, and testosterone levels were used to evaluate testicular function in men at baseline, end of treatment, and during 5 years of follow-up.

RESULTS A total of 145 women and 424 men, enrolled between May 19, 2011, and April 29, 2014, were included. The risk of premature ovarian insufficiency (FSH > 24 IU/L) and of having a low ovarian reserve (anti-müllerian hormone < 0.5 ng/mL) was reduced after treatment in the PET-driven group (odds ratio [OR], 0.20; 95% CI, 0.08 to 0.50; $P = .001$ and OR, 0.15; 95% CI, 0.04 to 0.56, $P = .005$, respectively). Both parameters were correlated with age and dose of alkylating agents. However, no significant differences were observed in terms of pregnancy rates. Men in the PET-driven group had a higher recovery rate of sperm parameters after treatment compared with the standard BEACOPP_{escalated} group, as well as a lower risk of severe testicular damage (OR, 0.26; 95% CI, 0.13 to 0.5; $P < .0001$) and a higher likelihood of achieving pregnancy (OR, 3.7; 95% CI, 1.4 to 9.3; $P = .004$).

CONCLUSION Although both treatments affected ovarian reserve and spermatogenesis, the PET-driven strategy decreased the risk of gonadal dysfunction and infertility in advanced Hodgkin lymphoma.

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ASSOCIATED
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INTRODUCTION

Hodgkin lymphoma (HL) is not only the most common cancer diagnosed in the adolescent and young adult population but also one of the most curable forms of cancer. In advanced-stage disease, chemotherapy with six cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP and BEACOPP_{escalated}), developed by the German Hodgkin Study Group, has demonstrated superiority in terms of progression-free survival (PFS) compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)–based therapy and has also been shown to have overall survival (OS) benefits in a meta-analysis.¹ However, this regimen

results in a higher risk of immediate and long-term toxicities, including infertility.²⁻⁴ Current guidelines recommend informing all young patients about the potential gonadal toxicity of chemotherapy and referring patients at high risk for fertility preservation procedures.^{5,6} However, individual assessment of the risk of gonadal dysfunction is complex and must take into account multiple factors such as chemotherapeutic agents and age.⁷ Prospective data on the impact of chemotherapy on ovarian reserve, sperm quality, and fertility remain scarce while essential for improving fertility counseling.

The prospective randomized noninferiority AHL2011 trial proposed a new de-escalated positron emission

CONTEXT

Key Objective

To prospectively evaluate the benefit in terms of gonadal function recovery and fertility of a de-escalated positron emission tomography (PET)–driven strategy using the low-intensity doxorubicin, bleomycin, vinblastine, and dacarbazine regimen in high-risk Hodgkin lymphoma patients with a negative PET scan after two upfront standard bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP_{escalated}) cycles (AHL2011 trial).

Knowledge Generated

Although complete gonadal function recovery was not observed after 5 years of follow-up, women had five-fold reduced risk of premature ovarian insufficiency and a higher ovarian reserve, when treated with de-escalated PET-driven strategy compared with standard six cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP_{escalated}) regimen. In men, sperm parameter and hormonal recovery rates were also higher in patients who switched to the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen, leading to an increased chance of achieving spontaneous pregnancy.

Relevance

These data provide a benchmark to facilitate discussions between patients with Hodgkin lymphoma and their physicians around the effects of various treatment strategies on long-term fertility, an important variable for many patients in the choice of treatment.

tomography (PET)–driven strategy in patients with advanced-stage HL to reduce treatment-associated toxicities. The authors showed that the use of the ABVD regimen after two cycles of induction with BEACOPP_{escalated} in early responders was safe while minimizing toxicities (ClinicalTrials.gov identifier: [NCT01358747](https://clinicaltrials.gov/ct2/show/study/NCT01358747)).⁸ Here, we provide data on fertility and gonadal damage in a prospective subcohort of young patients with HL recruited in the AHL2011 trial.

METHODS

Study Design and Participants

The present cohort was recruited from participants in an open-label, multicenter, prospective noninferiority randomized phase III trial (AHL2011). Eligible patients for AHL2011 were age 16–60 years, with newly diagnosed advanced HL (Ann Arbor disease stage III, IV, or IIB with a mediastinum-to-thorax ratio of 0.33 or greater or extranodal localization and an Eastern Cooperative Oncology Group performance status score < 3), excluding lymphocyte predominant subtype, and hypermetabolic lesions visible in baseline PET scan. Complete eligibility criteria were previously described.⁸ All female and male patients age 45 years or younger who participated in the AHL2011 trial were recruited for this gonadal function and fertility substudy.

The study was approved by the French and Belgian health authorities, the Ethics Committee of Dijon hospital, and the institutional review boards in each Belgian center. Informed consent was signed by all participants before starting treatment.

Procedures

After validation of the eligibility criteria, patients were randomly assigned to receive standard treatment (standard

arm) or de-escalated PET-driven treatment (study arm). All the patients first received two cycles of upfront BEACOPP_{escalated} (10 mg/m² bleomycin, 1.4 mg/m² vincristine, 600 mg/m² etoposide, 35 mg/m² doxorubicin, 1,250 mg/m² cyclophosphamide, 700 mg/m² procarbazine, and 560 mg/m² prednisone given by cycle) before performing a second PET scan (PET2). Patients allocated to the standard arm continued with two additional cycles of BEACOPP_{escalated}, irrespective of the PET2 results. Patients in the study arm switched to ABVD (25 mg/m² doxorubicin, 10 mg/m² bleomycin, 6 mg/m² vinblastine, and 375 mg/m² dacarbazine given twice/cycle) if the PET2 was negative, whereas if the PET2 was positive, they continued with two additional cycles of BEACOPP_{escalated}. After a total of four chemotherapy cycles, a third PET scan was performed before treatment completion with two additional cycles of BEACOPP_{escalated} or ABVD, according to the arm, if negative, or salvage therapy, if positive.

For the fertility substudy, serum was collected at baseline, at the end of treatment, and every year during 5 years of follow-up. Ovarian function was assessed by measurement of serum levels of follicle-stimulating hormone (FSH), estradiol, and anti-müllerian hormone (AMH). Sperm analysis was assessed locally, and FSH and testosterone measurements were performed.

All serum AMH measurements were centralized to the Laboratoire Hospitalier Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium, using Elecsys AMH Plus (Roche diagnosis, Germany) with a limit of detection of 0.01 ng/mL, whereas FSH, estradiol, and testosterone levels were measured locally for the majority of patients or in the Laboratoire Hospitalier Universitaire de Bruxelles using residual serum when data were not available.

Data on pregnancies, fertility treatments, and oncologic outcomes were collected for all patients at each time point.

Outcomes

The primary outcome was to compare the fertility parameters in both arms, including acute and long-term gonadal damage and pregnancy.

In women, premature ovarian insufficiency (POI) was defined as FSH threshold values of 25 IU/L or more at least twice, when available, during the follow-up.⁹ A low ovarian reserve was defined by AMH upper values of 0.5 ng/mL during the follow-up. Previous studies have calculated a model-based OR for early menopause of 23 for an AMH level of 0.5 ng/mL compared with an AMH level of 2 ng/mL.¹⁰ Ovarian function recovery was considered when FSH reached values below 25 IU/L during the follow-up or if the patients reported pregnancies. Women with FSH > 24 IU/L at inclusion or no data on pregnancy nor on hormonal values during the follow-up were excluded from analysis. In men, sperm quality was classified on the basis of WHO 2010 criteria defining a lower fifth percentile limit of 15×10^6 spermatozoa/mL and 40% total mobility.¹¹ Azoospermia was defined by the absence of spermatozoa in the ejaculate and severe oligospermia by a concentration of less than 5×10^6 spermatozoa/mL. An upper limit of FSH of 15 IU/L was defined as severe gonadal dysfunction in men.¹² Men with no data on hormonal values nor on pregnancy or sperm analysis were excluded from analysis.

Statistics

Statistics were performed using STATA/IC 16.0 software for Windows. All categorical variables are presented as proportions and percentages, and they were compared between groups with Pearson's chi square or Fisher's exact tests when appropriate. Continuous variables with non-normal distribution are presented as medians (P25-P75) and are compared between groups with the Mann-Whitney test (hormonal values), whereas those with normal distribution are presented as means (standard deviation) and are compared between groups with Student's *t* test (age, body mass index, and chemotherapy doses). Considering the presence of missing data during the follow-up and to simplify the figures, we pooled the data of hormonal levels during the follow-up. The latest value was taken into consideration for analysis if data at the two pooled time points were available. The groups have been compared at each time point first to confirm that the results were similar (Appendix Table A1, online only). Hormonal levels were compared between groups using the Mann-Whitney test and between time points using the Wilcoxon paired test. The percentage of recovery for AMH and FSH values was compared between time points by using the McNemar test. Univariate logistic regression models were used to study the association between POI and poor ovarian reserve in women and severe testicular damage in men according to

groups and exploratory variables such as age, body mass index, type and dose of chemotherapy, and fertility preservation in women. In women, two or three variables were entered into the multivariable logistic models on the basis of the number of cases and the significant results in the univariate models (group, age, and fertility preservation procedure for POI and group and age for low ovarian reserve). The Hosmer and Lemeshow test was used to check the goodness of fit of the model. Odds ratios with 95% CIs were derived from each variable coefficient in the final model. The significance of each coefficient was tested by the Wald test. The ovarian function recovery curves were assessed using the Kaplan-Meier method and compared by group using the logrank test. The HR and its 95% CI were derived from the univariate Cox model and the *P* values corresponding to the Wald test. The results were considered as significant when *P* < .05.

RESULTS

The AHL2011 trial enrolled 823 patients newly diagnosed with advanced HL from May 19, 2011, to April 29, 2014, at 90 centers in Belgium and France. A total of 145 female and 424 male patients were eligible for the analysis (Fig 1). The population characteristics were similar in both groups (Table 1).

In accordance with the Protocol (online only), patients in the study group either completed BEACOPP_{escalated} or switched to ABVD cycles after two cycles of upfront BEACOPP_{escalated} according to the result of the PET2, whereas all patients in the standard group continued BEACOPP_{escalated} cycles (Fig 1). Only 34 patients (11.9%) had positive PET2 and continued with BEACOPP_{escalated} cycles in the study group.

As expected, patients in the study group received significantly fewer cumulative doses of alkylating agents within a shorter timeframe (Table 1). They were more likely to complete the treatment and to receive the full dose of their chemotherapy regimen (64% v 43.3%, respectively; *P* = .01 in the female cohort and 70.7% v 58.8%, respectively; *P* = .01 in the male cohort). A total of 277 patients (97.5%) received a cumulative dose of cyclophosphamide $\geq 5,000$ mg in the standard group, whereas this high cumulative dose was reached only for 91 patients (32%) in the study group (patients who switched to BEACOPP_{escalated} or had a body surface area ≥ 1.9) (Table 1).

Fertility preservation was offered to 44.8% of women and 70% of men before starting chemotherapy (Table 1). Women who underwent fertility preservation were younger and more likely to be nulliparous at the time of diagnosis (Appendix Table A2, online only).

Ovarian function was normal and similar between groups before treatment but became significantly different during follow-up with higher levels of FSH and lower AMH levels in the standard group compared with the study group (Fig 2).

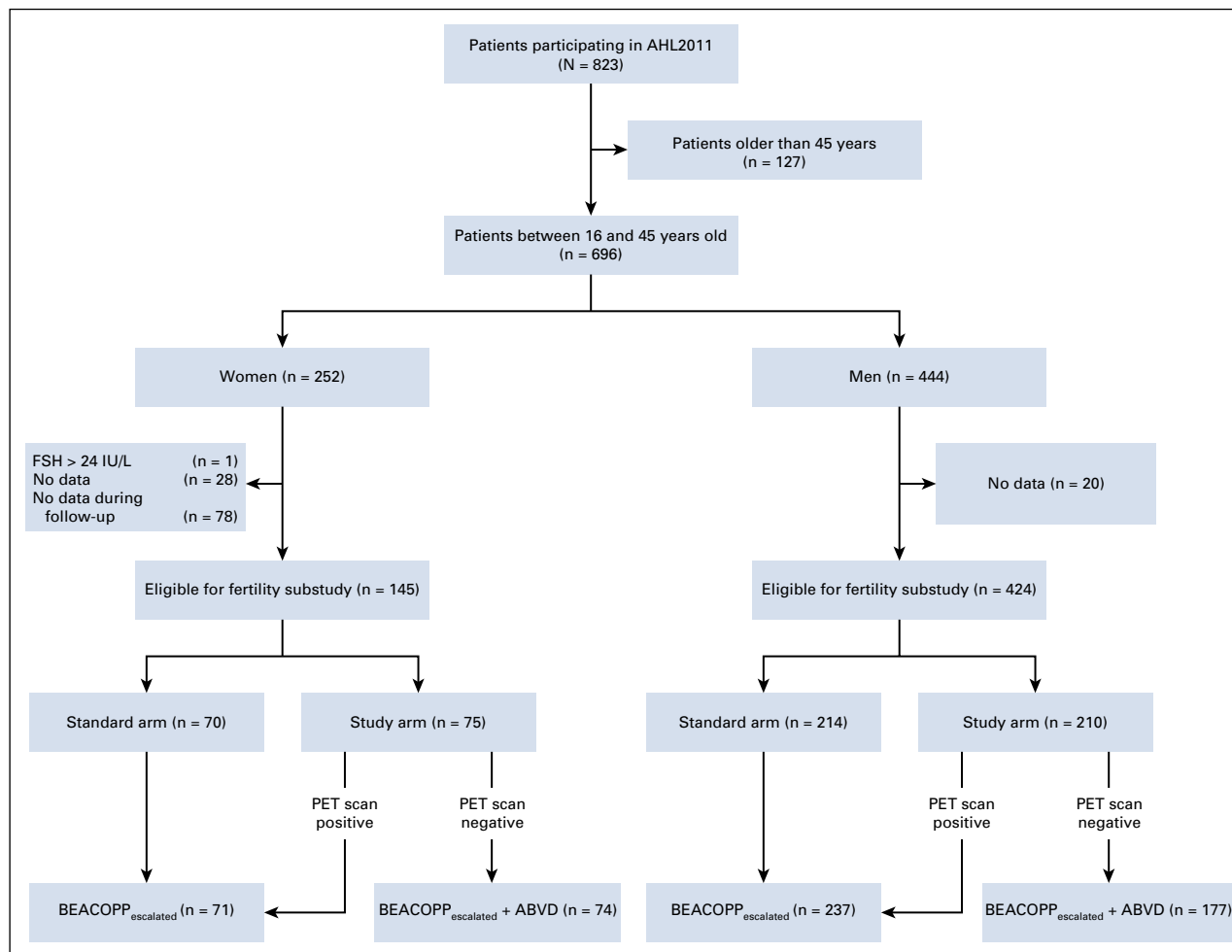


FIG 1. Study profile: AHL2011 participants and eligibility for the fertility substudy. All patients received two cycles of upfront BEACOPP_{escalated}. Patients in the study group either completed four BEACOPP_{escalated} or switched to ABVD cycles according to the result of the PET scan after two BEACOPP_{escalated} cycles, whereas all patients in the standard group continued BEACOPP_{escalated} cycles. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FSH, follicle-stimulating hormone; PET, positron emission tomography.

However, complete return to baseline levels was not reached at the end of follow-up (Appendix Table A3, online only). Overall, 46.1% versus 14.5% of the patients were considered to have POI in standard and study groups, respectively. The risk of POI was positively associated with increasing age, the absence of fertility preservation procedure, and cumulative dose of alkylating agents and was reduced in the study group (odds ratio [OR], 0.20, 95% CI, 0.08 to 0.50; $P = .001$) (Appendix Table A4, online only). After adjustment for age, the OR remained significant for the risk of POI (aOR, 0.09, 95% CI, 0.03 to 0.32; $P < .001$). Low ovarian reserve was significantly associated with standard group (OR, 0.15, 95% CI, 0.04 to 0.56; $P = .005$), older age, and high cumulative doses of alkylating agents (Appendix Table A4). Similarly, ovarian function recovery occurred more frequently in the study group (HR, 2.52, 95% CI, 1.73 to 3.67; $P < .0001$) (Appendix Fig A1, online only). After 2 years of follow-up,

proportions were 42.6% (95% CI, 31.7 to 55.6) and 73.7% (95% CI, 63.1 to 83.3) for standard and study groups, respectively ($P < .00001$).

In the male cohort, 179 sperm analyses including numeration were available at inclusion. No differences were observed in sperm parameters before treatment, but a total of 33 men (18.4%) had severe oligospermia, including five azoospermia. After treatment, sperm recovery was more frequently observed in the study group than in the standard group (Fig 3). After a median of 29 (24–35) months of follow-up, azoospermia was observed in 26 of 27 (96.3%) and 7 of 21 (33.3%) patients in the standard and study groups, respectively ($P = .008$). Testicular damage was associated with higher FSH values in the standard group during the follow-up (Fig 4 and Appendix Table A4). However, as for women, return to baseline FSH levels and sperm concentration values was not observed at the end of the follow-up (Appendix

TABLE 1. Characteristics of the Population at Baseline of Women and Men Participating in the AHL2011 Fertility Substudy and Treatment Characteristics According to Group

Demographic, Pathology, and Treatment Characteristics	Women			Men		
	Standard Group (n = 70)	Study Group (n = 75)	P	Standard Group (n = 214)	Study Group (n = 210)	P
Age, years						
Mean (SD)	26.7 (6.6)	26.9 (6.6)	.89	29.4 (7.7)	28.9 (7.3)	.47
Median (P25-P75)	25 (22-31)	27 (22-31)		29 (23-36)	27 (24-35)	
Mean BMI (SD)	22.8 (4.9)	22.9 (4.5)	.89	22.8 (4.1)	23 (3.6)	.51
Previous parity, No.	69	75		202	199	
> 0, No. (%)	24 (34.8)	24 (32)	.72	83 (41.1)	79 (39.7)	.78
Fertility preservation procedure, No. (%)	32 (46.4)	33 (44)	.72	154 (73.3)	143 (70.1)	.47
Contraceptive, No.	67	73	.38			
User at diagnosis, No. (%)	61 (91)	63 (86.3)				
Ann Arbor stage, No. (%)						
I	0	1 (1.3)	.36	0	0	.80
II	15 (21.4)	10 (13.3)		24 (11.2)	26 (12.4)	
III	18 (25.7)	17 (22.7)		59 (27.6)	62 (29.5)	
IV	37 (52.9)	47 (62.7)		131 (61.2)	122 (58.1)	
Treatment received, No. (%)						
BEACOPP _{escalated}	70 (100)	1 (1.3)	NA	214 (100)	33 (15.7)	NA
BEACOPP _{escalated} + ABVD	0 (0)	74 (98.7)		0 (0)	177 (84.3)	
Mean duration of chemotherapy (SD), days	111.5 (20.2)	150.2 (24.1)	< .0001	114 (113-120)	149 (127-155)	< .0001
Mean cumulative dose mg (SD)	70	75		214	210	
Cyclophosphamide-N	11,036 (2,431)	4,282 (1,214)	< .0001	13,188 (2,434)	5,814 (2,934)	< .0001
Dose	70	75		214	210	
Etoposide-N	5,267 (1,232)	2,047 (589)	< .0001	6,325 (1,169)	2,798 (1,416)	< .0001
Dose	70	75		214	210	
Procarbazine-N	6,329 (1,356)	2,339 (778)	< .0001	7,405 (1,496)	3,316 (1,727)	< .0001
Dose	70	75		213	210	
Vincristine-N	10.6 (2.3)	4.1 (0.98)	< .0001	11.2 (2.4)	4.95 (2.6)	< .0001
Dose (SD)	70	75		212	210	
Bleomycin-N	87.6 (21.1)	162.7 (20.6)	< .0001	103.5 (20.8)	157 (53.2)	< .0001
Dose (SD)	0	74		4	161	
Vinblastine-N	0	75.3 (16.2)		11 (7.3)	87.8 (13.6)	< .0001
Dose (SD)	0	74		0	162	
Dacarbazine-N	0	4,897 (797)		0	5,569 (788)	
Dose (SD)	70	75		214	210	
Doxorubicin-N	320.1 (66.4)	448.3 (46.9)	< .0001	375 (69)	451 (63)	< .0001
Dose (SD)						
Relapse, No. (%)	3 (4.3)	2 (2.6)	.67	29 (13.5)	31 (14.7)	.78

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BMI, body mass index; NA, not applicable; SD, standard deviation.

Table A3). No difference in testosterone levels was observed at inclusion and during follow-up between the groups (Fig 4).

A total of 58 women, 29 in each group, conceived after treatment and reported 76 live births (Table 2). Women who conceived were more likely to achieve spontaneous

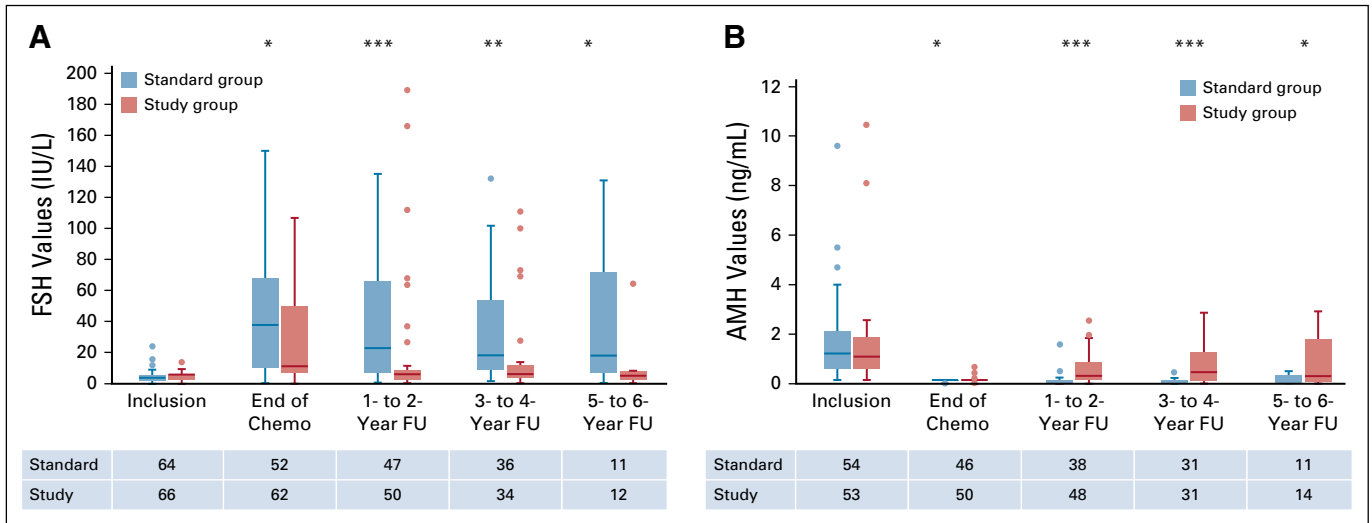


FIG 2. Hormonal profile of women per treatment group. (A) FSH values. (B) AMH values. The number of serum samples analyzed at each time point is reported under each figure. Data after 1-2 years, 3-4 years, and 5-6 years were pooled. Boxes represent median and interquartile range. Bars are SEs, and points are outliers. Standard versus study groups: * $P < .05$, ** $P < .01$, and *** $P < .001$. AMH, anti-müllerian hormone; chemo, chemotherapy regimen; FSH, follicle-stimulating hormone; FU, follow-up.

pregnancies in the study group than in the standard group, but the difference was not significant (Table 2). Only 26 men (6.1%) reported pregnancies after treatment, but there was a clear benefit of de-escalated PET-driven strategy in terms of fertility (OR, 3.7; 95% CI, 1.4 to 9.3; $P = .004$) (Table 2). Moreover, survivors treated with the standard regimen were more likely to achieve pregnancy after assisted reproductive technology (ART).

DISCUSSION

This AHL2011 subanalysis demonstrated the advantage of de-escalated PET-driven treatment for reducing gonadal toxicity in young high-risk patients, without impairing oncologic outcomes.⁸ In women, POI and low ovarian reserve were less frequently observed in the study compared with the standard group. A previous study showed that AMH levels decreased significantly during chemotherapy in patients with lymphoma, but women who were treated with the ABVD regimen had a higher likelihood of recovering their AMH level than those treated with non-ABVD regimens.¹³ The usefulness of this marker for evaluating ovarian function in lymphoma survivors was demonstrated in the RATHL and German Hodgkin Study trials.^{14,15} These studies showed a correlation between AMH levels after treatment and the type of regimen as well as age. The AMH level before treatment is also a predictor of long-term ovarian function,¹⁶ but its correlation with the ability to achieve spontaneous pregnancy after treatment remains controversial.¹⁷ In the HD14 study, significantly lower median AMH level was observed after two cycles of BEACOPP_{escalated} plus two cycles of ABVD (2 + 2) compared with four cycles of ABVD, whereas it was not associated

with a lower chance of motherhood after 42 months of follow-up.¹⁸ However, it was established that better recovery of the AMH levels is associated with a long-term benefit in terms of ovarian function and probably fertility.¹⁹

In AHL2011, FSH levels increased at the end of chemotherapy but decreased thereafter in the PET-driven arm. Notably, although recovery of FSH and AMH levels was observed during the follow-up in the PET-driven arm, they did not completely return to baseline levels at inclusion as it was previously described after ABVD regimen alone.¹⁴ In RATHL trial, 93% of the women in ABVD group recovered normal ovarian function after two years of follow-up compared with 73% in AHL2011 study group. Nevertheless, the AHL2011 fertility substudy showed that patients receiving more than two cycles of BEACOPP had a significantly higher risk of POI compared with those who received two cycles of BEACOPP followed by ABVD regimen, demonstrating the advantage of the PET-driven strategy to reduce ovarian damage in these high-risk patients. As for RATHL trial, the differences in the POI rate and in the ovarian reserve were not reflected in the fertility potential of women as no difference was observed in the number of patients who achieved pregnancies after treatment although patients in the standard group tended to use more ART. Long-term follow-up is required to confirm a potential benefit of this strategy on fertility in women.

In men, abnormal sperm is frequently observed before oncologic therapy in patients diagnosed with HL, with only 20%-75% of the patients having normal sperm parameters.²⁰ We confirmed these findings as almost 20% of the men were diagnosed with severe oligospermia before treatment. Nevertheless, we demonstrated the benefit of

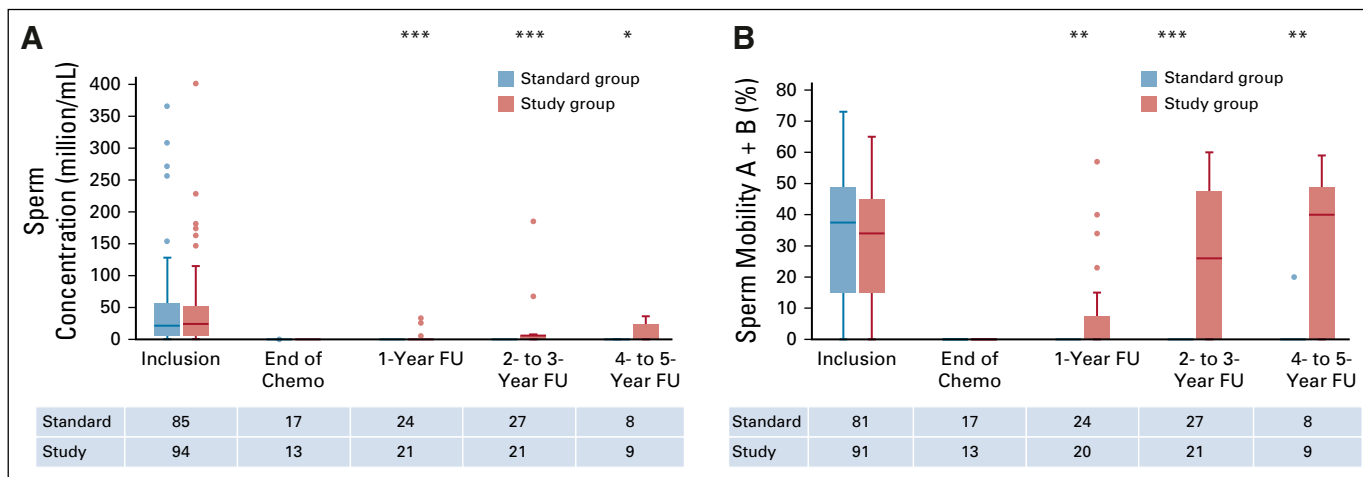


FIG 3. Sperm characteristics of men per treatment group. (A) Number of sperm cells per mL in semen. (B) Percentage of progressive sperm (rapid-A plus slow-B progressive mobility). The number of samples analyzed at each time point is reported under each figure. Data after 2-3 years and 4-5 years of FU were pooled. Boxes represent median and interquartile range. Bars are SEs, and points are outliers. Standard versus study groups: * $P < .05$, ** $P < .01$, and *** $P < .001$. Chemo, chemotherapy regimen; FU, follow-up.

the PET-driven strategy, providing a significant improvement in sperm parameters and a high rate of recovery of normal FSH levels. Importantly, this option had a significant impact on fertility, as we observed a higher chance to conceive even when the use of cryopreserved sperm was excluded from the analysis. Large prospective studies on reproductive function in patients with lymphoma are also scarce in men. A recent systematic review including five studies analyzed the effect of the ABVD and BEACOPP regimens on male reproductive function. The large majority of patients treated with BEACOPP face azoospermia with only a 4% recovery rate in patients with dyspermia.²¹ In this AHL2011 subanalysis, 96% and 33% of men were azoospermic after 2 years of follow-up in the standard and the

PET-driven groups, respectively, demonstrating the clear benefit of this strategy even if two cycles of upfront BEACOPP_{escalated} are administered before switching to the ABVD regimen. Nevertheless, the upfront cycles of alkylating-based regimen in the de-escalated PET-driven strategy induced more testicular damage than ABVD alone (escalated PET-driven strategy), after which only 0%-4% of azoospermia was observed after 2 years.²⁰

This large substudy demonstrated the major impact of this new therapeutic strategy on the patients' future quality of life. Despite more unfavorable disease characteristics at baseline in the AHL2011 study compared with the RATHL study¹⁴ (Ann Arbor stage III-IV: 88% v 58%, International Prognostic Score > 3 31% v 17.4%), the AHL2011 strategy

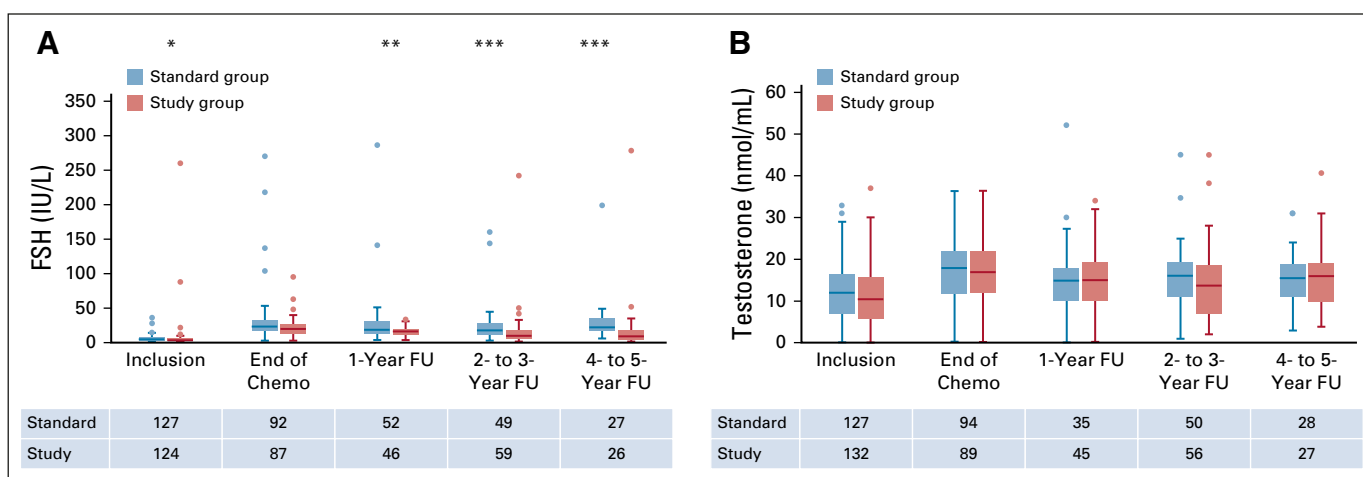


FIG 4. Hormonal profile of men per treatment group. (A) FSH values. (B) Testosterone values. The number of serum samples analyzed at each time point is reported under each figure. Data after 2-3 years and 4-5 years of FU were pooled. Boxes represent median and interquartile range. Bars are SEs, and points are outliers. Standard versus study groups: * $P < .05$, ** $P < .01$, and *** $P < .001$. Chemo, chemotherapy regimen; FSH, follicle-stimulating hormone; FU, follow-up.

TABLE 2. Conception and Pregnancy Outcomes in Women and Men Participating in the AHL2011 Fertility Substudy According to Group

Conception and Pregnancy Parameters	Women			Men		
	Standard Group (n = 70)	Study Group (n = 75)	P	Standard Group (n = 214)	Study Group (n = 210)	P
Patients with at least one pregnancy, No. (%) ^a	29 (41.4)	29 (38.6)	.65	6 (2.8)	20 (9.5)	.004
Total No. of pregnancies	37	39		7	22	.004
Mean time to pregnancy after treatment (SD), months	30.3 (14.3)	26.4 (17.1)	.35	35 (16.3)	32.6 (15.6)	.75
Mean age at pregnancy (SD), years	27.2 (3.5)	27.7 (5.0)	.65	32.5 (4)	31.9 (3.7)	.73
Conception, No. (%) ^b						
Spontaneous	21 (72.4)	26 (89.7)	.13	1 (16.7)	11 (55)	.26
ART	4 (13.8)	0		4 (66.7) ^c	7 (35) ^c	
Unknown	4 (13.8)	3 (10)		1 (16.7)	2 (10)	
Delivery, No. (%) ^b						
None	5 (17.2)	7 (23.3)	.35	0 (0)	1 (5)	1
One live birth	21 (72.4)	17 (58.6)		5 (83.3)	16 (80)	
Two live births	2 (6.9)	5 (17.2)		1 (16.7)	3 (15)	
Three live births	1 (3.5)	0		0	0	

Abbreviations: ART, assisted reproductive technology; SD, standard deviation.

^aNo. of pregnancies per total No. of patients included.

^bType of conception and No. of live births per pregnant women.

^cIncluding one conception using cryopreserved sperm.

provides better patient outcomes in terms of PFS and OS in both PET2-positive (3-year PFS: 70.7% v 67.5% and 3-year OS: 99% v 97) and PET2-negative patients (3-year PFS: 91.8% v 85% and 3-year OS: 93.9% v 87.8%) even if cross trial comparison must be taken with caution. So, the difference of gonadal function recovery in female observed between the two studies, in favor of the RATHL study, has to be balanced with the chance of reaching long-term HL control to determine the best individual strategy. However, as no marker is available at baseline to accurately predict the risk of PET2 positivity, which requires switch from ABVD to BEACOPP in the RATHL approach, fertility preservation counseling should be proposed in male and female when either RATHL or AHL2011 strategies are applied in routine practice.

The main limitation of the study remains the missing data. This issue was also encountered in other studies²² and is probably the main reason for the scarcity of prospective reproductive data in cancer survivors, especially outside the field of gynecology. Additional efforts should be strengthened to systematically consider gonadal toxicity as

a secondary end point in oncologic trial involving young male and female patients.¹⁹

Nevertheless, this AHL2011 subanalysis provides unique data on the risk of gonadal dysfunction after treatment in both women and men and enhances the cost-effectiveness of this approach.²³ It reinforces the need to refer all of them for fertility counseling before starting their chemotherapy regimen, especially in women as less than half of them underwent fertility preservation procedure. In men, the use of cryopreserved sperm is relatively limited in cancer survivors, but sperm cryopreservation is a simple procedure offering at least a similar live birth rate after ART than in the non-cancer population.²⁴

In conclusion, the AHL2011 PET-driven strategy in patients with advanced HL seems to reduce the risk of acute POI by five times in young women compared with the standard regimen. Although our data suggested that this strategy also has beneficial effect on fertility, it should be confirmed by larger studies with long-term follow-up.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Gonadal Function Recovery in Patients With Advanced Hodgkin Lymphoma Treated With a PET-Adapted Regimen: Prospective Analysis of a Randomized Phase III Trial (AHL2011)**

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APPENDIX

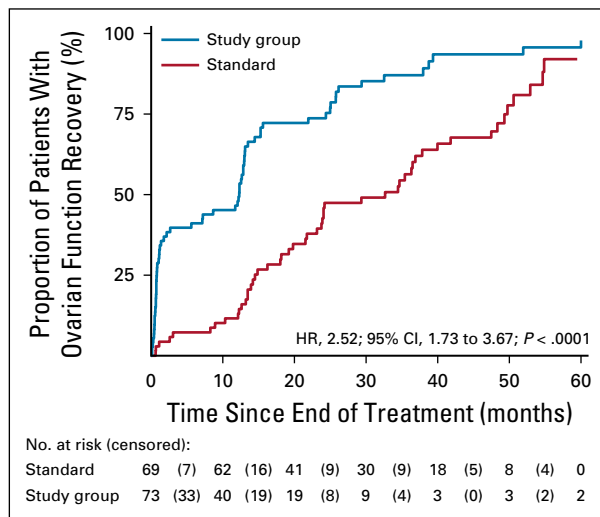


FIG A1. Recovery of the ovarian function (FSH level < 25 IU/L or pregnancy) after the end of the treatment: Kaplan-Meier curves showed recovery per groups. FSH, follicle-stimulating hormone; HR, hazard ratio.

TABLE A1. Hormonal and Sperm Values at Each Time Point Expressed as Median (P25-P75) in Women and Men

Hormonal and Sperm Values	Inclusion	End of Chemo	1-Year FU	2-Year FU	3-Year FU	4-Year FU	5-Year FU	6-Year FU
Women								
FSH (IU/L)								
Standard group								
No.	64	52	40	31	28	22	11	2
Median	3.95	38	35.5	32.6	21.3	16.1	19	4.95
P25	2	11.31	14.5	7	10.85	6.55	7.93	0.3
P75	5.5	68	71	69.6	53.35	44.1	72	9.6
Study group								
No.	65	62	46	35	30	22	10	3
Median	4	11.35	6.39	6.1	5.56	7.8	4.22	7.89
P25	2	7	3.6	4.2	3.35	5.2	2.94	5.2
P75	6	50	11.6	8.2	9.9	14	5.74	8.39
<i>P</i>	.61	.02	< .0001	.0004	.0001	.18	.009	1.0
AMH (ng/mL)								
Standard group								
No.	54	46	31	23	20	23	11	2
Median	1.2	0.15	0.15	0.03	0.03	0.03	0.03	0.40
P25	0.64	0.15	0.03	0.03	0.03	0.03	0.03	0.35
P75	2.09	0.15	0.15	0.113	0.156	0.136	0.15	0.46
Study group								
No.	53	50	43	32	27	22	11	4
Median	1.1	0.15	0.3	0.32	0.57	0.35	0.26	2.07
P25	0.64	0.15	0.15	0.13	0.21	0.12	0.05	0.88
P75	1.8	0.15	1.1	0.77	1.01	1.01	0.57	2.77
<i>P</i>	.28	.02	< .0001	< .0001	< .0001	.0007	.07	.35
Men								
FSH (IU/L)								
Standard group								
No.	127	92	52	34	35	24	7	
Median	5	23.5	18.9	16.8	17	22.15	41	
P25	3	18	12.65	13	12	16.15	21	
Study group								
No.	124	87	46	49	43	23	11	
Median	4	20	16.25	12	9.9	8.86	12.8	
P25	2.42	12.5	12.1	5.5	6	4.6	4.7	
P75	6	26	20	21.5	16	15	34.4	
<i>P</i>	.02	.003	.05	.01	.001	.0003	.07	
Testosterone (nmol/mL)								
Standard group								
No.	127	94	53	35	35	24	8	
Median	12	17.9	14.92	14	15.2	15	16	
P25	7	12	11	10.5	10.7	10.5	10.1	
P75	16.4	22	18	18	19	18.45	19.5	
(continued on following page)								

TABLE A1. Hormonal and Sperm Values at Each Time Point Expressed as Median (P25-P75) in Women and Men (continued)

Hormonal and Sperm Values	Inclusion	End of Chemo	1-Year FU	2-Year FU	3-Year FU	4-Year FU	5-Year FU	6-Year FU
Study group								
No.	132	89	46	45	40	23	12	
Median	10.48	17	15	15.5	14.7	15	16.5	
P25	5.9	12	10.34	11	10.66	10	13.48	
P75	15.5	21.98	19.1	20.11	19	19	20.3	
<i>P</i>	.25	.88	.75	.61	.68	.74	.79	
Sperm concentration (spermatozoa × 10 ⁶ /mL)								
Standard group								
No.	85	17	24	24	10	6	2	
Median	21.7	0	0	0	0	0	0.26	
P25	6	0	0	0	0	0	0.02	
P75	55.2	0	0	0	0	0.02	0.5	
Study group								
No.	94	13	21	19	7	9	1	
Median	24.15	0	0	0.12	5.4	0.58	1.54	
P25	6.3	0	0	0	1.25	0.36	1.54	
P75	52	0	0.02	4.3	8	14	1.54	
<i>P</i>	.92	1.0	.006	< .0001	.0001	.05	.22	

Abbreviations: AMH, anti-müllerian hormone; chemo, chemotherapy; FSH, follicle-stimulating hormone; FU, follow-up.

TABLE A2. Fertility Preservation in Women Participating in the AHL2011 Substudy on Fertility

Population and Procedure Characteristics	Fertility Preservation (n = 65)	No Fertility Preservation (n = 79)	P
Age, years			.003
Mean age (SD)	25.5 (4.8)	28.3 (7.5)	
Median (P25-P75)	24 (22-29)	27 (22-35)	
Nulliparity, No. (%)	52 (81.3)	43 (54.4)	.001
Ann Arbor stage, No. (%)			.39
< 4	25 (38.5)	36 (45.6)	
4	40 (61.5)	43 (54.4)	
Procedure, No. (%)			
Ovarian tissue cryopreservation	30 (46.2)	NA	
Oocyte or embryo cryopreservation	13 (20)		
GnRH agonist	8 (12.3)		
Combined procedure	6 (9.2)		
Unknown	8 (12.3)		

NOTE. Population of women who underwent fertility preservation was compared with the women who did preserve the fertility for age, parity, and Ann Arbor stage of the diseases. Procedures were described for the women who underwent fertility preservation.

Abbreviations: GnRH, gonadotropin-releasing hormone; NA, not available; SD, standard deviation.

TABLE A3. Gonadal Function Recovery at the End of FU on the Basis of FSH (IU/L) and AMH (ng/mL) Values in Women and on the Basis of FSH (IU/L), Testosterone (nmol/mL), and Sperm Concentration (No. of Spermatozoa $\times 10^6$ /mL) Values in Men

Hormonal Values	Standard Group					Study Group				
	No.	Median FU Time (months)	Inclusion	End of FU	<i>P</i> ^a	No.	Median Time of FU (months)	Inclusion	End of FU	<i>P</i> ^a
Women										
FSH	49	40.1 (27.6-49.9)	4 (2-6)	20.1 (9.6-53)	< .0001	54	38.7 (24.5-50.7)	4 (2-6)	7.85 (3.9-14)	< .0001
AMH	41	48.2 (24.2-54.8)	1.2 (0.5-1.9)	0.031 (0.03-0.15)	< .0001	48	46.8 (28.6-60.1)	1.2 (0.6-1.8)	0.28 (0.1-1.2)	< .0001
Men										
FSH	55	34.1 (15.5-48.5)	5 (3.1-9)	18 (12.3-29)	< .0001	56	36.7 (24.5-48.7)	3.7 (2.4-5.6)	12 (5.6-18.4)	< .0001
Testosterone	52	35.3 (15.8-48.3)	12 (8-17.2)	16 (11-18.2)	.05	54	36.8 (24-50.1)	11 (5.8-15)	14 (10-18)	.03
Sperm	25	29.3 (22.2-36.7)	27.5 (14.5-51.3)	0 (0-0)	< .0001	27	26.2 (23.1-42.4)	36.8 (11-82)	0.1 (0-14)	.0001

NOTE. Values are expressed as median (P25-P75) and compared with baseline levels at inclusion in the standard and the study groups.

Abbreviations: AMH, anti-müllerian hormone; FSH, follicle-stimulating hormone; FU, follow-up.

^aWilcoxon for paired samples.

TABLE A4. Odds Ratios of Gonadal Dysfunction According to the Different Parameters Evaluated in Women and Men During the FU

Parameters Evaluated	Women		Men
	POI	Low Ovarian Reserve	Testicular Dysfunction
Study v standard group	0.20 (0.08 to 0.50), $P = .001$	0.15 (0.04 to 0.56), $P = .005$	0.26 (0.13 to 0.50), $P < .0001$
Fertility preservation procedure Yes v no	0.29 (0.09 to 0.07), $P = .008$	0.47 (0.17 to 1.3), $P = .15$	
Age, years	1.2 (1.1 to 1.3), $P < .0001$	1.3 (1.1 to 1.4), $P < .0001$	1.04 (0.99 to 1.08), $P = .14$
BMI, kg/m ²	0.92 (0.82 to 1.03), $P = .14$	0.98 (0.87 to 1.1), $P = .82$	0.99 (0.92 to 1.09), $P = .95$
Cyclophosphamide cumulative dose < 5,000 mg v $\geq$ 5,000 mg	0.23 (0.09 to 0.59), $P = .002$	0.13 (0.04 to 0.50), $P = .003$	0.20 (0.09 to 0.42), $P < .0001$
Procarbazine cumulative dose < 5,000 mg v $\geq$ 5,000 mg	0.23 (0.09 to 0.55), $P = .001$	0.11 (0.02 to 0.49), $P = .004$	0.21 (0.11 to 0.42), $P < .0001$
Etoposide cumulative dose < 5,000 mg v $\geq$ 5,000 mg	0.23 (0.10 to 0.56), $P = .001$	0.07 (0.008 to 0.51), $P = .01$	0.22 (0.11 to 0.44), $P < .0001$

NOTE. Parameters included the groups, the fertility preservation procedure, the age, the BMI, and chemotherapeutic agents (cyclophosphamide, procarbazine, and etoposide). Premature ovarian insufficiency is defined as FSH $\geq$ 25 IU/L, low ovarian reserve is defined as AMH < 0.5 ng/mL, and testicular dysfunction is defined as FSH $\geq$ 15 IU/L. The results are expressed as odds ratio (95% CI) and P values.

Abbreviations: AMH, anti-müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone; FU, follow-up; POI, premature ovarian insufficiency.