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ORIGINAL REPORT

# Contemporarily Treated Patients With Hodgkin Lymphoma Have Childbearing Potential in Line With Matched Comparators

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## ABSTRACT

### Purpose

With excellent cure rates for young patients with Hodgkin lymphoma (HL), there is an increasing number of female survivors of HL interested in becoming pregnant. Here, we report childbearing among contemporarily treated HL survivors in comparison with the general population.

### Material and Methods

Using Swedish registers, 449 women (ages 18 to 40 years) diagnosed with HL between 1992 and 2009 and in remission 9 months after diagnosis were identified. Patients were age- and calendar-year–matched to 2,210 population comparators. Rates of first postdiagnosis childbirth were calculated. Hazard ratios (HRs) with 95% CIs were estimated for different follow-up periods using Cox regression. Cumulative probabilities of first childbirth were calculated in the presence of the competing risk of death or relapse.

### Results

Twenty-two percent of relapse-free patients with HL had a child during follow-up, and first childbirth rates increased over time, from 40.2 per 1,000 person-years (1992 to 1997) to 69.7 per 1,000 person-years (2004 to 2009). For comparators, childbirth rates remained stable (70.1 per 1,000 person-years). Patients diagnosed between 2004 and 2009 had a cumulative probability of childbirth similar to comparators. Three years or more after diagnosis, no differences in childbirth rates were observed between patients and comparators, regardless of stage or treatment. Patients who received six to eight courses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone had a lower childbirth rate than comparators during the first 3 years (HR, 0.23; 95% CI, 0.06 to 0.94), as did patients who received six to eight courses of chemotherapy and radiotherapy (HR, 0.21; 95% CI, 0.07 to 0.65).

### Conclusion

Childbearing potential among female survivors of HL has improved over time, and childbirth rates 3 years after diagnosis in contemporarily treated patients are, in the absence of relapse, similar to those in the general population, regardless of stage and treatment.

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## INTRODUCTION

The childbearing potential of survivors of Hodgkin lymphoma (HL) is of considerable interest because the disease affects young women, prognosis is excellent, and assisted reproductive methodologies continuously develop. Trends in childbearing over calendar time and treatments can provide caregivers with insight in how to counsel patients about their future fertility and family planning.[1]

Historically, treatments for HL with the potential to cure have had negative effects on fertility.[2-7] Irradiation to the pelvic region,[8] alkylating agents, and the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen are particularly gonadotoxic.[7,9,10] As treatments have developed over time, the negative effect on fertility has become less pronounced. Studies of patients treated with more modern regimens, such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD),[11] bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), or combinations of the two,[9,10,12,13] have shown BEACOPP to be more gonadotoxic than

ASSOCIATED CONTENT

Appendix
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ABVD. The actual childbearing among women treated with six to eight courses of ABVD or BEACOPP is still not fully known,[14] especially not in relation to childbirth rates in the general population.

Most investigations of childbearing after HL rely on self-reported questionnaires.[6,7,10-13] Whereas questionnaire-based studies can be affected by selection bias,[6,7,10-13] this is of less concern in register-based settings. Registers, however, often lack detailed clinical information. Previous register-based studies evaluating childbirth patterns have indicated a lower number of children born to patients with HL than comparators,[4,15,16] but have not assessed childbearing by currently used treatments in a population-based setting.

In this study, we supplemented data from national registers with information from medical records to study childbearing and time to first childbirth after HL diagnosis among patients treated according to contemporary guidelines. Because treatment after relapse is associated with high infertility risk, we limited the analysis to relapse-free follow-up time and evaluated childbearing in patients who only received first-line treatment. Furthermore, we investigate how childbirth rates change over time since diagnosis.

## MATERIAL AND METHODS

### Data Sources and Study Population

We identified all female patients with HL (according to the 7th revision of the International Classification of Diseases [ICD], ICD-7, code 201) diagnosed in Sweden between 1992 and 2009, ages 18 to 40 years at diagnosis, with a record in the nationwide Swedish Cancer Register (SCR). The SCR was established in 1958, and reporting is mandatory by law for both clinicians and pathologists/cytologists, resulting in $>$ 95% completeness.[17] Because clinical information is not recorded in the SCR, additional information was retrieved from clinical registers and medical records as previously described,[18,19] using record-linkage via the personal identification number assigned to all Swedish residents. In total, 472 female patients with HL were identified. Relapses were assessed through medical records or codes of autologous/allogeneic stem-cell transplantations in the National Patient Register (NPR), which has records of visits to inpatient care since 1964, with national coverage since 1987).[19,20] The NPR was also used to retrieve infertility diagnoses (ICD-10, code N97) and/or in vitro fertilization (IVF; ICD-10, code Z31) for a subset of patients diagnosed from 2001 to 2009 (when the NPR also recorded visits to outpatient specialist care). Post-HL infertility was defined as any infertility/IVF diagnosis recorded more than 6 months after HL diagnosis. Fertility referral/preservation was defined as having an infertility/IVF diagnosis within 2 months before and 6 months after diagnosis.

Five female comparators per patient were randomly sampled from the Register of Total Population and Population Changes[21] matched by birth year and being alive, in Sweden, and free from HL at the time of the corresponding diagnosis of the patient with HL (index date). From here on, diagnosis date shall be interpreted as index date for the comparators.

Information on childbirths was retrieved from the Swedish Medical Birth Register, which includes data on all live births since 1973.[22] Between January 1973 and June 2008, all stillbirths delivered after 28 full gestational weeks, and since July 2008, all stillbirths after 22 gestational weeks were also included. Abortions (spontaneous/elective/therapeutic) are not registered. Dates of migrations and death were added using the Register of Total Population and Population Changes and the Cause of Death Register.

Patients who were pregnant at diagnosis (n = 10), had primary progressive disease (n = 10), or relapsed within 9 months after diagnosis (n = 3) were excluded, resulting in a patient cohort comprising 449 women. Comparators who were pregnant at index date (n = 126) were also excluded, leaving 2,210 comparators.

### Treatment

Throughout the study period, patients were treated according to national guidelines.[23-27] Between 1992 and 1996, two to four courses of MOPP-ABV were used for limited-stage HL (Ann Arbor stages IA to IIA), and from 1997, two to four courses of ABVD were standard. For patients with advanced stages (Ann Arbor stages IIB to IVB), six to eight courses of chemotherapy were used, with corresponding transition from MOPP-ABV to ABVD. Patients with comorbidities could receive LVPP-OEPA (chlorambucil, vinblastine, procarbazin, and prednisone alternating with vincristine, etoposide, prednisone, and doxorubicin), ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone), or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Since 1998, patients with advanced stage and an International Prognostic Score $>$ 2 were treated with six to eight courses of BEACOPP-14 or BEACOPP-escalated. If the International Prognostic Score was $\leq$ 2, six to eight courses of ABVD were administered.[28] Radiotherapy (RT) was given to patients with limited-stage disease or in advanced stages if the patient initially had bulky disease, slow tumor regression, or residual disease after the end of chemotherapy. Fewer patients received RT after full chemotherapy (six to eight courses) between 2004 and 2009 than between 1998 and 2003.[19] Patients who were primary progressive or had a relapse were administered second-line chemotherapy, followed by high-dose chemotherapy with autologous stem-cell support in responding patients.[29]

### Statistical Methods

The outcome was time to first childbirth (including stillbirth) after diagnosis. Time since diagnosis was the underlying time scale in all analyses and follow-up (expressed in terms of person-years) started 9 months after diagnosis. Patients with HL and comparators were followed until the date of first childbirth, relapse, emigration, death, or December 31, 2010, whichever came first. Follow-up was restricted to the first 7 years after diagnosis to avoid different lengths of follow-up between calendar periods. Childbirth rates (with 95% CIs constructed using the quadratic approximation to the Poisson log-likelihood for the log rate) and frequencies were calculated for patients with HL and comparators overall and by calendar period, age at diagnosis, and parity status at diagnosis. For patients, they were also calculated by clinical stage at diagnosis, treatment, chemotherapy regimen, and number of courses, and whether the patient received RT. Hazard ratios (HRs) with 95% CIs were estimated from Cox regression models stratified by patient/comparator set, thus adjusting for the matching variables. Patients with missing information on any variable in the model were excluded. All models were adjusted for time since diagnosis (time scale) and included an interaction between the patient with HL (yes/no) and the variable at hand. One set of models assumed proportional hazards, estimating one HR across the entire follow-up, and another estimated separate HRs for two distinct follow-up periods (9 months to 3 years and 3 to 7 years after diagnosis) in a model assuming proportional hazards within each period. In addition, a flexible parametric survival model[30] (with 2 degrees of freedom for the baseline rate and the time-dependent effect) was used to estimate childbirth rates as smooth functions of follow-up time.

The cumulative probability of first childbirth within 7 years was calculated nonparametrically (by integrating the product of the overall survival function and the cause-specific hazard) in the presence of the competing risk of relapse/death.[31] All statistical analyses were performed using STATA version 14/15 software (StataCorp, College Station, TX). The study was approved by the regional ethics review board in Stockholm, Sweden.

## RESULTS

### Childbirth Overall

Among the 449 patients with HL, 101 (22.5%) had a childbirth during follow-up (rate, 57.2 per 1,000 person years). For the 2,210 comparators, the corresponding number was 638 (28.9%;

rate, 70.1 per 1,000 person-years; Table 1). The distribution of parity at diagnosis/matching was similar among patients with HL (36.1%) and comparators (36.5%). The mean follow-up time was 3.9 years (range, 9 days to 6.2 years) for patients and 4.1 years (range, 1 day to 6.2 years) for comparators. Patients had a lower childbirth rate in relation to comparators over the full follow-up (HR, 0.78; 95% CI, 0.63 to 0.97), mainly driven by the lower rate during the first 3 years (HR, 0.58; 95% CI, 0.41 to 0.81; Table 2). After 3 years, the difference in childbirth rate between patients and comparators was negligible. Follow-up was censored at date of relapse, but none of the 45 relapsed patients had a child between the date of relapse and the study period's last date.

### Childbirth Over Calendar Period

The childbirth rate among patients increased over calendar time (Table 2), whereas for comparators, it remained stable (Fig A1, online only). Patients diagnosed from 1992 to 1997 had a lower rate than comparators over the full follow-up (HR, 0.51; 95% CI, 0.30 to 0.87) and even more so during the first 3 years (HR, 0.34; 95% CI, 0.18 to 0.64). For patients diagnosed during the last calendar period, childbirth rates were comparable between patients with HL and comparators (overall HR, 0.93; 95% CI, 0.66 to 1.33). These patients also reached a level in cumulative probability of first childbirth similar to comparators (Fig 1).

### Childbirth by Age, Stage, and Treatment

In both age groups, patients had a lower childbirth rate than comparators during the first 3 years (Table 2). After 3 years, there was no difference. Changing the age groups to 18 to 29 and 30 to 40 yielded similar results (overall HR, 0.81; 95% CI, 0.64 to 1.03; and HR, 0.67; 95% CI, 0.42 to 1.08, respectively). The distribution of limited and advanced stage was equal among all patients with HL

**Table 1.** Frequencies and Childbirth Rates With 95% CIs Postdiagnosis for Female Patients With HL Diagnosed From 1992 to 2009 at Ages 18 to 40 Years and Matched Comparators

| Characteristic | Patients With HL | | | Matched Comparators | | |
|---|---|---|---|---|---|---|
| | No. (%) | No. of Childbirths (%) | Childbirth Rate* (95% CI) | No. (%) | No. of Childbirths (%) | Childbirth Rate* (95% CI) |
| Overall | 449 (100) | 101 (22.5) | 57.2 (47.1 to 69.5) | 2,210 (100) | 638 (28.9) | 70.1 (64.9 to 75.8) |
| Year of diagnosis | | | | | | |
| 1992-1997 | 76 (16.9) | 15 (19.7) | 40.2 (24.2 to 66.6) | 380 (17.2) | 135 (35.5) | 71.3 (60.2 to 84.4) |
| 1998-2003 | 177 (39.4) | 48 (27.1) | 56.7 (42.7 to 75.2) | 876 (39.6) | 304 (34.7) | 69.3 (61.9 to 77.5) |
| 2004-2009 | 196 (43.7) | 38 (19.4) | 69.7 (50.7 to 95.8) | 954 (43.2) | 199 (20.9) | 70.7 (61.5 to 81.2) |
| Age at diagnosis, years | | | | | | |
| 18-25 | 221 (49.2) | 59 (58.4) | 64.4 (49.9 to 83.2) | 1,085 (49.1) | 337 (52.8) | 73.5 (66.0 to 81.7) |
| 26-40 | 228 (50.8) | 42 (41.6) | 49.4 (36.5 to 66.9) | 1,125 (50.9) | 301 (47.2) | 66.8 (59.6 to 74.7) |
| Parity status at diagnosis | | | | | | |
| Nulliparous | 287 (63.9) | 72 (25.1) | 61.8 (49.0 to 77.8) | 1,404 (63.5) | 405 (28.9) | 68.5 (62.2 to 75.5) |
| Parous | 162 (36.1) | 29 (17.9) | 48.3 (33.6 to 69.6) | 806 (36.5) | 233 (28.9) | 73.2 (64.3 to 83.2) |
| Stage | | | | | | |
| Limited (IA-IIA) | 221 (49.2) | 55 (24.9) | 61.5 (47.2 to 80.1) | — | — | — |
| Advanced (IIB-IVB) | 228 (50.8) | 46 (20.2) | 52.8 (39.5 to 70.5) | — | — | — |
| Treatment and courses | | | | | | |
| 2 to 4 courses of chemotherapy with RT | 170 (37.9) | 43 (25.3) | 60.9 (45.2 to 82.1) | — | — | — |
| 6 to 8 courses of chemotherapy without RT | 168 (37.4) | 35 (20.8) | 62.3 (44.7 to 86.8) | — | — | — |
| 6 to 8 courses of chemotherapy with RT | 90 (20.0) | 18 (20.0) | 43.8 (27.6 to 69.5) | — | — | — |
| Other† | 16 (3.6) | 3 (18.8) | 45.2 (14.6 to 140.2) | — | — | — |
| Missing | 5 (1.1) | 2 (40.0) | — | — | — | — |
| Chemotherapy and courses | | | | | | |
| 2 to 4 ABVD | 141 (31.4) | 34 (24.1) | 61.5 (44.0 to 86.1) | — | — | — |
| 6 to 8 ABVD | 152 (33.9) | 32 (21.1) | 61.8 (43.7 to 87.4) | — | — | — |
| 2 to 4 MOPP-ABV(D) | 19 (4.2) | 6 (31.6) | 66.3 (29.8 to 147.5) | — | — | — |
| 6 to 8 MOPP-ABV(D) | 32 (7.1) | 9 (28.1) | 65.7 (34.2 to 126.4) | — | — | — |
| 6 to 8 BEACOPP | 55 (12.3) | 10 (18.2) | 43.1 (23.2 to 80.1) | — | — | — |
| LVPP-OEPA, ChlVPP, or CHOP | 25 (5.6) | 1 (4.0) | 7.38 (1.04 to 52.4) | | | |
| Other‡ | 20 (4.5) | 7 (35.0) | 87.7 (41.8 to 184.0) | — | — | — |
| Missing | 5 (1.1) | 2 (40.0) | — | — | — | — |
| RT | | | | | | |
| No | 181 (40.3) | 38 (21.0) | 62.4 (45.4 to 85.8) | — | — | — |
| Yes | 268 (59.7) | 63 (23.5) | 54.4 (42.5 to 69.7) | — | — | — |

NOTE. Follow-up was restricted to the first 7 years. Diagnosis date should be interpreted as index date for the matched comparators. Due to rounding, not all percentages add up to 100.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HL, Hodgkin lymphoma; LVPP-OEPA, chlorambucil, vinblastine, procarbazine, prednisone alternating with vincristine, etoposide, prednisone, doxorubicin; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; RT, radiotherapy.

*Per 1,000 person-years.

†Among which eight patients (50%) were treated with two to four courses of chemotherapy and no RT, and eight patients (50%) were treated with only RT.

‡Among which 12 patients (60%) were treated with another chemotherapy regimen and eight patients (40%) were treated with only RT.

  

**Table 2.** HRs With 95% CIs Comparing Postdiagnosis Childbirth Rates of Female Patients With HL Diagnosed From 1992 to 2009 at Ages 18 to 40 Years With Those Among Matched Comparators

| Characteristic | Patients With HL Versus Matched Comparators (reference) | | |
|---|---|---|---|
| | HR* (95% CI) | HR† (95% CI) | |
| | 9 Months to 7 Years | 9 Months to 3 Years | 3 to 7 Years |
| Overall | **0.78 (0.63 to 0.97)** | **0.58 (0.41 to 0.81)** | 0.99 (0.75 to 1.31) |
| Year of diagnosis | | | |
| 1992-1997 | **0.51 (0.30 to 0.87)** | **0.34 (0.18 to 0.64)** | 0.64 (0.36 to 1.10) |
| 1998-2003 | 0.81 (0.59 to 1.10) | **0.56 (0.36 to 0.85)** | 1.03 (0.72 to 1.45) |
| 2004-2009 | 0.93 (0.66 to 1.33) | 0.72 (0.47 to 1.08) | 1.32 (0.87 to 2.02) |
| Age at diagnosis, years | | | |
| 18-25 | 0.85 (0.64 to 1.13) | **0.61 (0.41 to 0.93)** | 1.03 (0.75 to 1.41) |
| 26-40 | **0.70 (0.50 to 0.97)** | **0.55 (0.37 to 0.82)** | 0.93 (0.62 to 1.38) |
| Parity status at diagnosis | | | |
| Nulliparous | 0.85 (0.66 to 1.10) | **0.62 (0.41 to 0.92)** | 1.01 (0.75 to 1.36) |
| Parous | **0.66 (0.44 to 0.98)** | **0.55 (0.35 to 0.86)** | 0.90 (0.55 to 1.48) |
| Stage | | | |
| Limited (IA-IIA) | 0.81 (0.61 to 1.08) | **0.63 (0.41 to 0.98)** | 1.01 (0.70 to 1.46) |
| Advanced (IIB-IVB) | 0.74 (0.55 to 1.01) | **0.52 (0.31 to 0.87)** | 0.97 (0.66 to 1.43) |
| Treatment | | | |
| 2 to 4 courses of chemotherapy with RT | 0.80 (0.58 to 1.10) | 0.64 (0.39 to 1.05) | 0.96 (0.63 to 1.46) |
| 6 to 8 courses of chemotherapy without RT | 0.86 (0.60 to 1.23) | 0.69 (0.40 to 1.17) | 1.06 (0.66 to 1.72) |
| 6 to 8 courses of chemotherapy with RT | **0.59 (0.36 to 0.96)** | **0.21 (0.07 to 0.65)** | 0.95 (0.55 to 1.65) |
| Other‡ | 1.00 (0.30 to 3.31) | — | — |
| Chemotherapy and courses | | | |
| 2 to 4 ABVD | 0.84 (0.59 to 1.20) | 0.57 (0.31 to 1.02) | 1.14 (0.73 to 1.81) |
| 6 to 8 ABVD | 0.85 (0.59 to 1.24) | 0.61 (0.34 to 1.08) | 1.17 (0.72 to 1.92) |
| 2 to 4 MOPP-ABV(D) | 0.76 (0.32 to 1.80) | 0.97 (0.28 to 3.33) | 0.63 (0.19 to 2.11) |
| 6 to 8 MOPP-ABV(D) | 1.07 (0.51 to 2.23) | 0.82 (0.24 to 2.79) | 1.26 (0.49 to 3.22) |
| 6 to 8 BEACOPP | 0.55 (0.29 to 1.04) | **0.23 (0.06 to 0.94)** | 0.84 (0.40 to 1.78) |
| LVPP-OEPA, ChlVPP, or CHOP | **0.10 (0.01 to 0.70)** | — | — |
| Other§ | 0.52 (0.25 to 1.09) | 0.78 (0.30 to 2.00) | 0.33 (0.10 to 1.09) |
| RT | | | |
| No | 0.88 (0.62 to 1.23) | 0.68 (0.40 to 1.14) | 1.11 (0.70 to 1.76) |
| Yes | **0.73 (0.56 to 0.96)** | **0.53 (0.34 to 0.82)** | 0.93 (0.67 to 1.31) |

NOTE. Follow-up was restricted to the first 7 years. Diagnosis date should be interpreted as index date for the matched comparators. For categories with fewer than five childbirths, only estimates from the proportional hazards model (ie, the first column) are presented. Bold type indicates statistically significant effects.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HL, Hodgkin lymphoma; HR, hazard ratio; LVPP-OEPA, chlorambucil, vinblastine, procarbazine, prednisone alternating with vincristine, etoposide, prednisone, doxorubicin; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; RT, radiotherapy.

*HRs were estimated from Cox regression models stratified on patient/comparator set. All models assumed proportional hazards, were adjusted for time since diagnosis (time scale) and the matching variables (year of diagnosis and age at diagnosis), and included an interaction between HL patient status (yes/no) and the variable at hand.

†HRs were estimated from Cox regression models stratified on patient/comparator set. Piecewise proportional hazards was assumed within each of the periods (9 months, 3 years) and (3 years, 7 years) after diagnosis date, enabling the effect of the variable at hand to differ between the two distinct periods. All models were adjusted for time since diagnosis (time scale) and the matching variables (year of diagnosis and age at diagnosis) and included an interaction between HL patient status (yes/no) and the variable at hand.

‡Among which eight patients (50%) were treated with two to four courses of chemotherapy and no RT, and eight patients (50%) were treated with only RT.

§Among which 12 patients (60%) were treated with another chemotherapy regimen and eight patients (40%) were treated with only RT.

(49.2% limited, 50.8% advanced; Table 1). During the first 3 years, patients with both limited- and advanced-stage disease had a lower childbirth rate than comparators (limited-stage HR, 0.63; 95% CI, 0.41 to 0.98; advanced-stage HR, 0.52; 95% CI, 0.31 to 0.87; Table 2). The effect was strongest during the two earliest calendar periods (Table A1, online only). After 3 years, childbirth rates across stages were comparable to those among the comparators. Childbirth rates over time since diagnosis were distinctly different between patients and comparators (Fig 2).

Chemotherapy changes over time are listed in Table 3. Childbirth rates in patients who received two to four or six to eight courses of ABVD were almost identical (61.5 and 61.8 per 1,000 person-years, respectively; Table 1), and no differences were observed between patients treated with ABVD and comparators (Table 2). Patients who received six to eight courses of BEACOPP had lower childbirth rates than comparators during the first 3 years (HR, 0.23; 95% CI, 0.06 to 0.94). Overall, patients treated with six to eight courses of chemotherapy together with RT had a lower childbirth rate (HR, 0.59; 95% CI, 0.36 to 0.96). The difference was more pronounced the first 3 years. A lower rate was also observed among patients treated with RT (with and without chemotherapy), although the effect was smaller (overall: HR, 0.73; 95% CI, 0.56 to 0.96; during the first 3 years: HR, 0.53; 95% CI, 0.34 to 0.82) and mainly observed in the two first calendar periods (data not shown). Among patients diagnosed from 1998 to 2009 and treated with two to four or six to eight courses of ABVD, the cumulative probability of a first childbirth approached and aligned with that of the comparators (Fig 3). Patients diagnosed during the same period

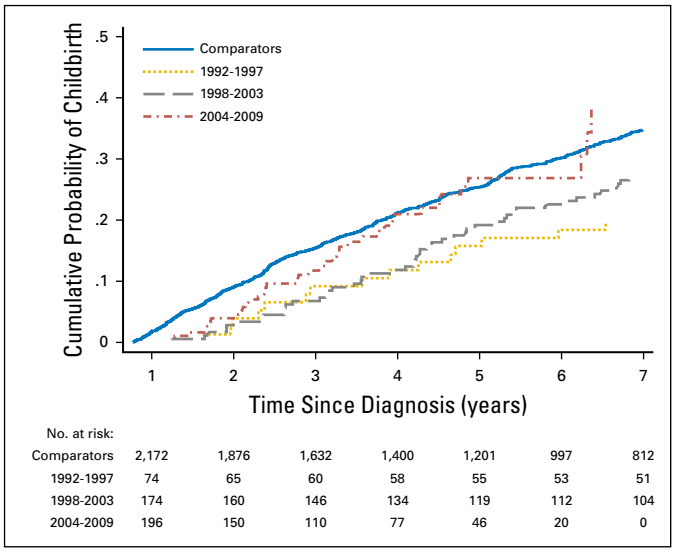


**Fig 1.** Cumulative probability of childbirth postdiagnosis, accounting for the competing event of death or relapse, among female patients with Hodgkin lymphoma diagnosed from 1992 to 2009, ages 18 to 40 years at diagnosis, during the first 7 years after diagnosis, by calendar period of diagnosis. The blue curve represents the cumulative probability of childbirth for the comparators for all calendar periods combined.

but treated with six to eight courses of BEACOPP also had an increasing (albeit lower than the comparators) cumulative probability of childbirth. Median age at diagnosis did not differ between patients treated with ABVD or BEACOPP.

### *Infertility Diagnoses and Fertility Preservation*

Twenty-nine (9.5%) of the 307 patients diagnosed between 2001 and 2009 had a recorded infertility/IVF diagnosis more than 6 months after HL diagnosis, of whom the majority (19 patients; 66%) had an infertility diagnosis. Even so, 10 (34.5%) of these women had a childbirth during follow-up (before [n = 3] and after [n = 7]the infertility diagnosis). Twenty women (6.5%) had fertility referral/preservation around the time of diagnosis. Among these patients, six (30.0%) had a recorded childbirth during follow-up, whereas for the remaining 287 patients, 71 (24.7%) had a childbirth during follow-up. Fertility referral/preservation was most common among patients who received six to eight courses of chemotherapy and no RT (10.6%).

## DISCUSSION

In this population-based study of childbearing among female survivors of HL, relapse-free women had birth rates similar to those in the general population from 3 years after diagnosis onward, regardless of stage and primary treatment. Even after treatment with the most gonadotoxic chemotherapy combination, BEACOPP, administered to patients with high-risk disease, childbirth rates, although reduced during the first 3 years, later approached those of the comparators. Birth rates and cumulative probabilities increased over calendar time. Thus, contemporarily treated patients with HL not encountering a relapse have childbearing potential similar to Swedish women in general. In contrast, none of the women who experienced relapse had a childbirth after relapse, underlining the importance of curative first-line treatment also from a fertility perspective.

The reduced childbirth rates during the first 3 years are in line with earlier results on patients with advanced-stage disease treated with escalated BEACOPP, where 51.9% had a desire to have children but only 15% reported parenthood 4 years after diagnosis.[12] This is not unexpected because fertility is reduced (temporary or permanent) as patients are undergoing treatment, there is a risk of relapse, and the focus is on getting healthy rather than having children. In this study, the observed increasing cumulative probability of childbirth over time since diagnosis, also in patients treated with BEACOPP, is therefore positive, indicating a recovery of fertility in many women. The high childbearing potential among patients with limited-stage disease is in line with results from Behringer et al,[13] who found birth rates in 331 survivors of early-stage unfavorable HL similar to the German population, and a smaller study where 36 limited-stage, 3-year relapse-free HL survivors treated with ABVD were compared with friend/sibling controls.[11] Still, a comparison of 1,654 survivors of HL (treated between 1964 and 2004) with 6,414 controls showed a slight but significantly lower number of

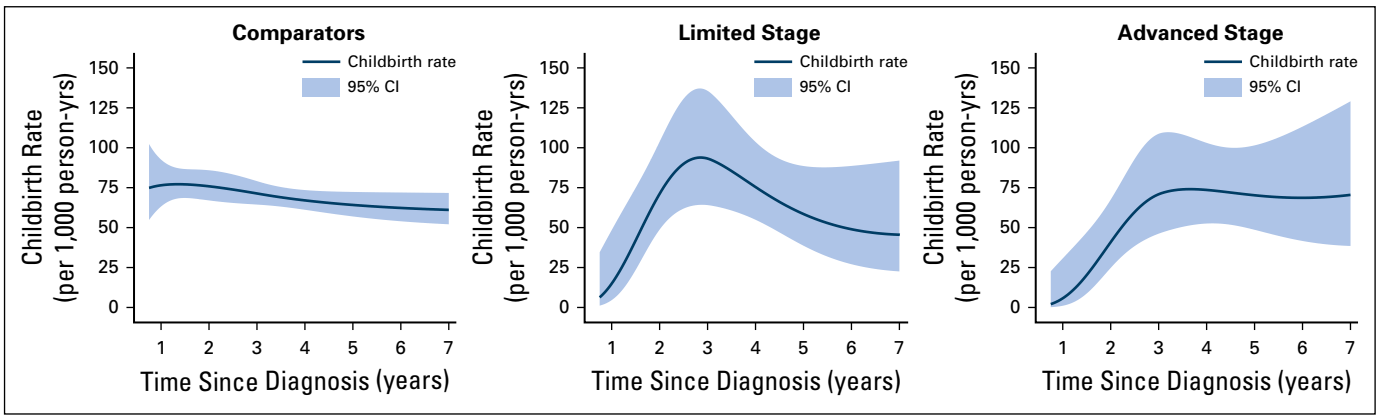


**Fig 2.** Estimated childbirth rates with 95% CIs postdiagnosis among female patients with Hodgkin lymphoma diagnosed between 1992 and 2009, ages 18 to 40 years at diagnosis, and matched comparators for the first 7 years after diagnosis/index date, by stage at diagnosis. Rates were modeled using a flexible parametric survival model with one interior knot for the baseline rate.

  

**Table 3.** Distribution of Chemotherapy Regimen, Including Number of Courses, Across the Study Period (1992-2009)

| Treatment | Median Age at Diagnosis (IQR) | Calendar Year of Diagnosis | | | Total No. (%) |
|---|---|---|---|---|---|
| | | 1992-1997, No. (%) | 1998-2003, No. (%) | 2004-2009, No. (%) | |
| Chemotherapy and courses | | | | | |
| 2 to 4 ABVD | 27 (22 to 33) | 0 (0.0) | 68 (38.4) | 73 (37.2) | 141 (31.4) |
| 6 to 8 ABVD | 25 (21 to 32) | 0 (0.0) | 58 (32.8) | 94 (48.0) | 152 (33.9) |
| 2 to 4 MOPP-ABV(D) | 23 (20 to 27) | 15 (19.7) | 4 (2.3) | 0 (0.0) | 19 (4.2) |
| 6 to 8 MOPP-ABV(D) | 24 (20 to 31) | 26 (34.2) | 6 (3.4) | 0 (0.0) | 32 (7.1) |
| 6 to 8 BEACOPP | 28 (24 to 32) | 2 (2.6) | 33 (18.6) | 20 (10.2) | 55 (12.3) |
| LVPP-OEPA, ChlVPP, or CHOP | 24 (20 to 31) | 24 (31.6) | 0 (0.0) | 1 (0.5) | 25 (5.6) |
| RT only | 24 (19 to 35) | 7 (9.2) | 1 (0.6) | 0 (0.0) | 8 (1.8) |
| Other | 23 (21 to 24) | 2 (2.6) | 3 (1.7) | 7 (3.6) | 12 (2.7) |
| Missing | 26 (21 to 32) | 0 (0.0) | 4 (2.3) | 1 (0.5) | 5 (1.1) |
| Total | 26 (21 to 32) | 76 (100) | 177 (100) | 196 (100) | 449 (100) |

NOTE. As a result of rounding, not all percentages add up to 100.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; IQR, interquartile range; LVPP-OEPA, chlorambucil, vinblastine, procarbazine, prednisone alternating with vincristine, etoposide, prednisone, doxorubicin; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; RT, radiotherapy.

children in survivors of HL.[10] A Norwegian study from 2011 also reported lower childbirth rates among female patients with HL,[16] as did a Swedish study from 2013.[32] However, these studies did not investigate childbirth rates as functions of time since diagnosis. Birth rates are expected to be low initially, and rates averaged over follow-up will not detect recovery of fertility or delays in childbearing. As shown here, there was a difference in childbirth rate shape between patients with limited- and advanced-stage disease (although nonsignificant). Patients with limited-stage disease, shorter treatment periods, and quicker recovery likely have their first postdiagnosis childbirth earlier, and because only first childbirths were included, a decline was seen.

Historically, the risk of infertility in women undergoing HL treatment has been of major concern.[6,12,13] The chemotherapy protocols primarily used in first-line therapy today are ABVD and BEACOPP. Although the previously most commonly used regimen MOPP is more gonadotoxic than ABVD, but not necessarily more than BEACOPP,[9,10,12,13,33,34] treatment with RT previously meant large irradiated volumes, sometimes also including the ovaries, increasing the risk of infertility.[8,28] Today, in case of subdiaphragmal limited-stage HL in close vicinity of the ovaries, two to four courses of chemotherapy and RT are often replaced with full chemotherapy and no RT.

The lower cumulative probability of childbirth among patients with HL diagnosed in the earlier calendar period indicates that changes in treatment may have affected fertility in this patient group. However, the observed improvements over time are likely multifactorial. No doubt, the less gonadotoxic treatments and improvements in survival[28] play a major role, but in addition, attitudes toward information, fertility counseling, and trends in society are likely important. Fear of relapse or fear of adverse consequences for the child might affect a female survivor's choice to have children.[7,10,19,35-37] In Sweden today, fertility counseling for women diagnosed with HL is recommended for patients with planned therapy of more than 4 months of ABVD, BEACOPP, or similar chemotherapy. Still, in our subset of patients diagnosed between 2001 and 2009, only 6.5% had undergone fertility referral/preservation. Similarly, a study from 2011 showed that only 9.5% of patients with breast cancer and lymphoma ages 20 to 29 years were referred to fertility counseling.[38] This raises the question of whether patients who need and wish to be referred to fertility counseling are offered this possibility. The results presented here are thus encouraging, especially for patients who need the most intensive first-line treatment and/or cannot undergo fertility preservation, because they reveal childbearing potential similar to women in general in a cohort where few patients underwent

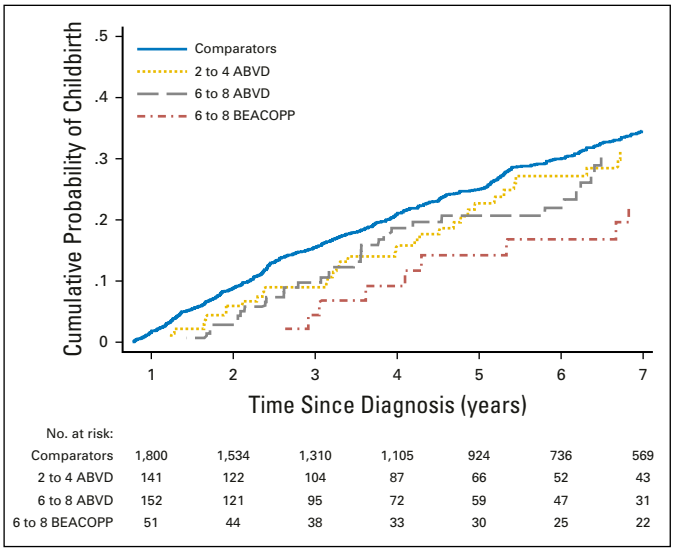


**Fig 3.** Cumulative probability of childbirth postdiagnosis, accounting for the competing event of death or relapse, among a subset of female patients with Hodgkin lymphoma diagnosed between 1998 (when doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP] were introduced) and 2009, ages 18 to 40 years at diagnosis, during the first 7 years after diagnosis date, by chemotherapy regimen and number of courses. The blue curve represents the cumulative probability of childbirth for the comparators (1998 to 2009).

fertility referral/preservation. Available fertility-preserving methods mainly include preservation of in vitro fertilized embryos, although cryopreservation of oocytes and cryopreservation of ovarian tissue can be performed.[39-42] Adjuvant gonadotropin-releasing hormone analogs have occasionally been administered,[9,43] although studies have not been able to prove their effectiveness.[34,43]

The high childbirth rates in patients treated with ABVD do not suggest a strong need for fertility preservation. However, patients who experience primary progressive disease and relapse receive recommendations for consolidative high-dose chemotherapy with stem-cell support, which carries a high risk of infertility. This was also confirmed here; no children were born after relapse. In light of this, fertility advice is still appropriate, given the difficulty to determine which patients will relapse and also considering the limited possibility of fertility preservation before relapse treatment initiation.

The major strength of our study is the use of population-based registers enriched with clinical data that enabled an evaluation of childbearing among patients treated according to modern principles, with a focus on relapse-free follow-up and stratification by treatment. The detailed information enabled estimation of the cumulative probability of first childbirth, taking competing risks of relapse/death into account. From the patient's perspective, this measure is likely of more interest than, for example, rates/rate ratios alone, because it represents the actual situation, given all possible events that may occur. Relapse information was obtained through medical records, complemented by recordings of stem-cell transplantations from the NPR. Using these different sources is a strength, but a few relapses might still have been missed. Also, despite the population-based approach, with inclusion of nearly all female patients in Sweden, the statistical power was somewhat limited.

In conclusion, the high childbirth rates across all treatment groups among young, relapse-free female survivors of HL are reassuring. The increase of childbirth rates over calendar time likely has a multifactorial explanation, reflecting reduced toxicity in HL treatment but also changes in attitudes and counseling. The good childbearing potential among contemporarily treated patients, as well as the safety of a pregnancy after HL (with no increased risk of relapse for the women[19] and reports of good health for children[35-37]), needs to be communicated to patients, because it can relieve unnecessary anxiety and concern. Because treatment of relapse is associated with a high risk of infertility, the importance of curative first-line treatment needs to be stressed, also from a fertility perspective.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Contemporarily Treated Patients With Hodgkin Lymphoma Have Childbearing Potential in Line With Matched Comparators**

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## Appendix

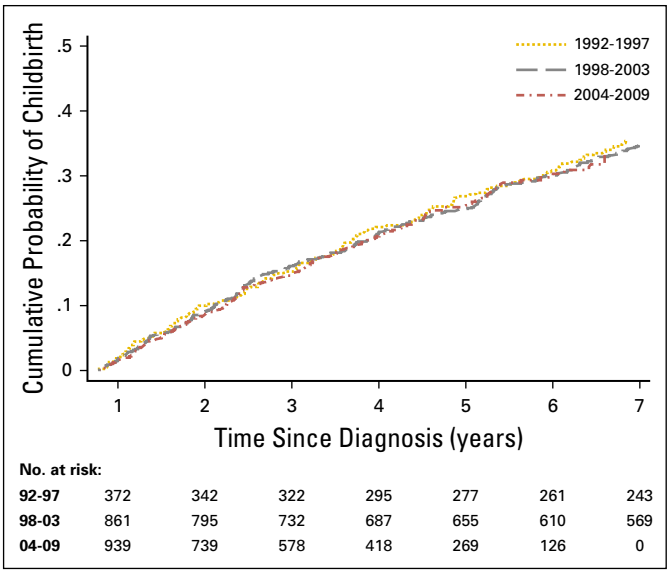


**Fig A1.** Cumulative probability of childbirth postdiagnosis (index date), accounting for the competing event of death, among the comparators by calendar period of diagnosis.

**Table A1.** Frequencies and Childbirth Rates With 95% CIs Postdiagnosis Among Female Patients With Hodgkin Lymphoma Diagnosed From 1992 to 2009 at Ages 18 to 40 by Stage and Calendar Year of Diagnosis

| | Year of Diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | 1992-1997 | | 1998-2003 | | 2004-2009 | |
| Characteristic | No. (%) | Childbirth Rate* (95% CI) | No. (%) | Childbirth Rate* (95% CI) | No. (%) | Childbirth Rate* (95% CI) |
| Comparators | 380 (83.3) | 71.3 (60.2 to 84.4) | 876 (83.2) | 69.3 (61.9 to 77.5) | 954 (83.0) | 70.7 (61.5 to 81.2) |
| Limited stage (IA-IIA) | 43 (9.4) | 50.6 (28.0 to 91.3) | 87 (8.3) | 57.3 (38.4 to 85.5) | 91 (7.9) | 77.5 (50.0 to 120.1) |
| Advanced stage (IIB-IVB) | 33 (7.2) | 25.7 (9.6 to 68.4) | 90 (8.6) | 56.0 (37.6 to 83.6) | 105 (9.1) | 62.7 (39.5 to 99.5) |

| | Patients With HL Versus Matched Comparators (reference) | | | | | |
|---|---|---|---|---|---|---|
| | HR† (95% CI) | | HR† (95% CI) | | HR† (95% CI) | |
| Characteristic | 9 Months to 3 Years | 3 to 7 Years | 9 Months to 3 Years | 3 to 7 Years | 9 Months to 3 Years | 3 to 7 Years |
| Limited stage (IA-IIA) | 0.50 (0.23 to 1.06) | 0.83 (0.43 to 1.61) | 0.60 (0.34 to 1.07) | 1.01 (0.63 to 1.63) | 0.72 (0.42 to 1.24) | 1.21 (0.68 to 2.17) |
| Advanced stage (IIB-IVB) | **0.18 (0.06 to 0.56)** | 0.37 (0.13 to 1.04) | **0.51 (0.27 to 0.95)** | 1.04 (0.64 to 1.68) | 0.71 (0.38 to 1.30) | 1.44 (0.80 to 2.59) |

NOTE. HRs with 95% CIs, comparing childbirth rates with those among matched comparators. Follow-up was restricted to the first 7 years after diagnosis date. Diagnosis date should be interpreted as index date for the matched comparators. As a result of rounding, not all percentages add up to 100. Bold type indicates statistically significant effects.

Abbreviations: HL, Hodgkin lymphoma; HR, hazard ratio.

*Per 1,000 person-years.

†HRs were estimated from a Cox regression model stratified on patient/comparator set. Piecewise proportional hazards was assumed within each of the periods (9 months, 3 years) and (3 years, 7 years) after diagnosis date, enabling the effect of stage to differ between the two distinct periods. The model was adjusted for time since diagnosis (time scale) and the matching variables (year of diagnosis and age at diagnosis) and included an interaction between the stage of patients with HL (comparator/limited/advanced) and calendar period of diagnosis.