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ORIGINAL ARTICLE

Pregnancy rate and outcome of pregnancies in long-term survivors of Hodgkin's lymphoma

Francesco Gaudio[1] · Claudia Nardelli[2] · Paola Masciandaro[2] · Tommasina Perrone[1] · Filomena Emanuela Laddaga[3] · Paola Curci[1] · Raffaella Depalo[2] · Ettore Cicinelli[2] · Giorgina Specchia[1]

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Abstract

Thanks to the increased number of young survivors of Hodgkin's lymphoma (HL), management of the pregnancies of women who have a history of exposure to chemotherapies and radiation therapy is becoming increasingly common. Many patients and clinicians are worried that pregnancy after the diagnosis of HL may increase the risk of relapse, despite a lack of empirical evidence to support such concerns. In the present study, we included 89 women diagnosed with HL between 2006 and 2015 under the age of 50 years, who were in complete remission and alive without relapse > 1 year after treatment. We determined the pregnancy rate, time to pregnancy, and the disease-free survival. We found no evidence of significant impairment of the fertility of female HL long-term survivors and no evidence that a pregnancy increases the relapse rate among women in remission from HL. Survivors of HL need to consider a range of factors when deciding on future reproduction.

Keywords Fertility · Pregnancy · Hodgkin

Introduction

Most females diagnosed with Hodgkin's lymphoma (HL) are of reproductive age, and as the average maternal age in many industrialized countries rises, the proportion of women diagnosed with HL before having children will increase [1, 2].

Improvements in survival and the use of less gonadotoxic treatments have led to an increasing number of survivors of HL who wish to become pregnant [3, 4].

Early studies revealed higher relapse and mortality rates in patients in whom HL was diagnosed during pregnancy. This finding suggested an association between pregnancy and disease progression, but results of subsequent studies have rejected these findings [5–7].

Pregnancy is a unique immune condition, featuring both proinflammatory components, which primarily occur in the first and third trimesters, and anti-inflammatory components, which primarily occur in the second trimester [8].

There are plausible biological mechanisms by which pregnancy might increase the risk of relapse. An inflammatory reaction with a Th2 profile predominance and an increased number of inhibitory regulatory T cells are considered essential for pregnancy, to prevent rejection of the fetus [9, 10].

In studies of the etiology of HL, skewing the T cell response toward a Th2-type microenvironment is believed to support B cell survival and thus induce tumor cell proliferation in HL. In turn, regulatory T cells, which are increased in pregnant women, are thought to suppress the tumor-protective cytotoxic T lymphocytes needed for early clearance of HL precursor cells [11, 12].

Given the clinical importance of this question, and the current lack of empirical evidence, we investigated women with HL treated with modern regimens in order to evaluate a possible impairment of fertility and any association between recent pregnancy and relapse.

✉ Francesco Gaudio
fragaudio@alice.it

[1] Department of Emergency and Organ Transplantation (D.E.T.O.), Hematology Section, University of Bari, Bari, Italy

[2] Department of Biomedical Science and Human Oncology, Obstetrics and Gynecology Unit, University of Bari, Bari, Italy

[3] Department of Emergency and Organ Transplantation (D.E.T.O.), Pathology Section, University of Bari, Bari, Italy

Patients and methods

This retrospective study was focused on 89 females, less than 50 years old, diagnosed with HL and treated at the University Hospital of Bari (Italy) from 2006 to 2015, who were in complete remission and alive without relapse > 1 year after treatment.

All the patients had signed informed consent to undergo treatment after the risk of chemotherapy and the various treatment options had been explained to them. No patients refused authorization to use their medical records for research. No patients were lost to follow-up.

All patients were clinically staged according to the Ann-Arbor system, with medical history, complete physical examination, blood counts, biochemical profile, chest X-ray films, PET/CT total body, computed tomography of the chest, abdomen and pelvis, and unilateral bone marrow biopsy. All patients presented for counseling on fertility preservation methods before receiving cytotoxic chemotherapy. The AMH serum level was measured from venous blood; normal range is 1–8 ng/mL (values < 1 ng/mL were regarded as demonstrating severely reduced ovarian reserves). None of the patients received ovarian protection with GNRH analogues; 23 patients (26%) underwent ovarian cryopreservation. In order to assess the women's family planning, a questionnaire was provided to patients during medical examination.

Clinical characteristics are listed in Table 1. Median age at diagnosis was 31 years (range 16–49), and 28 patients (31%) presented advanced stage (III–IV), 35 (39%) bulky disease, 25 (28%) presented B symptoms, and 16 (18%) extranodal disease.

First-line chemotherapy was adriamycin, bleomycin, vinblastin, and dacarbazine (ABVD) in all the patients. The median number of chemotherapy lines was 1 (1–5), 65 (73%) patients had undergone prior supradiaphragmatic radiotherapy, and none pelvic radiotherapy.

In 74 patients (83%), a single treatment line was administered and 15 (17%) had further lines. IGEV was primarily used as salvage chemotherapy in 13/15 patients (87%); 2 patients received BEACOPP escalated; 13/89 (15%) underwent autologous stem cell transplantation. Carmustine, etoposide, cytarabine, and melphalan (BEAM) were used as high-dose chemotherapy. Three patients (3%) underwent allogeneic stem cell transplantation.

Statistical analysis

The cumulative incidence of pregnancy was calculated using the Kaplan–Meier method.

Time to pregnancy (TTP) was calculated from the last chemotherapy to pregnancy. Disease-free survival (DFS) was defined as the time interval between the end of treatment and relapse. The estimation of DFS was performed by the Kaplan–Meier method.

Identification of the impact of pregnancy on DFS was based on the log-rank test.

Results

From 2006 to 2015, 89 females with HL, under the age of 50 years, were diagnosed at the University Hospital of Bari (Italy). Patient characteristics are shown in Table 1.

The median age of patients at last follow-up was 28 years (14–56 years). Median follow-up from last chemotherapy was 68 months (24–190 months).

Before the start of first-line chemotherapy, regular menstrual cycles were reported in 71 patients (80%) and irregular in 18 (20%); 58 patients (65%) patients resumed regular menstrual cycles (14/52 patients with hormone assistance). Median time to the resumption of regular menstruation was 9 months (1–54 months).

Measurement of anti mullerian hormone (AMH) levels showed a mean of 2.06 (1.52) ng/mL (range 0.05–6.51 ng/mL).

Pregnancies and their outcome

Among the 89 women with HL, 42 (47%) were nulliparous throughout follow-up, 37 (42%) were parous but had no

Table 1 Patients' characteristics

	Pregnant	Not pregnant	Tot
Tot	8 (9%)	81 (91%)	89 (100%)
Stage III–IV	1 (12%)	27 (33%)	28 (31%)
B symptoms	1(12%)	24 (30%)	25 (28%)
Bulky disease	1(12%)	34 (42%)	35 (39%)
Extranodal disease	0(0%)	16 (20%)	16 (18%)
Median chemotherapy number (range)	1 (1–3)	1 (1–5)	1 (1–5)
Autologous transplantation	1(12%)	15 (18%)	16 (18%)
Allogeneic transplantation	0	5 (6%)	4 (4%)
Regular menstrual cycle before treatment 71	7 (88%)	65 (80%)	72 (81%)

pregnancies during follow-up, and 8 (9%) developed pregnancy during follow-up (Table 2).

No pregnancy was observed in female patients older than 50 or in the first years after the end of treatment. No woman used cryopreserved oocytes.

The women who became pregnant during follow-up were represented in all the categories of demographic and clinical characteristics of initial disease, including advanced stage and presence of B symptoms (Table 1).

After a median follow-up of 5 years, 21 women (24%) had reached menopause (range 23–49 years; median 39 years). None of the parous women had tried to become pregnant; 15 women (17%) tried to become pregnant; 7/15 (47%) without success; 8/15 (53%) women became pregnant, giving birth to eight healthy children.

Detailed information on the eight women who got pregnant are shown in Table 3; 7 patients received a single line of chemotherapy (patients 1 to 7 received 4 cycles of ABVD followed by supradiaphragmatic radiotherapy; patient number 8 received 6 cycles of ABVD); one (patient number 4), who did not respond to first line, underwent autologous hematopoietic stem cell transplantation. The overall pregnancy rate was 9%. The median time from the end of the therapy to pregnancy was 42 months (range 32–92 months) and the cumulative incidence of pregnancy at 70 months was 11% (Fig. 1).

Median age at pregnancy was 32 years (range 27–36 years). One pregnant patient had achieved hormone-assisted ovulation, while the remaining patients had unassisted normal conception.

In total, 3 relapses occurred during follow-up: none occurred in recently pregnant women (Fig. 2). In one case (n.8), 3 months after the birth of the child, acute myeloid leukemia occurred with evidence of a complex karyotype, and the patient died.

Women exposed to a recent pregnancy had a lower relapse rate than that of not pregnant women, although this difference was not statistically significant.

Table 2 Pregnancy analysis

	N	%
Nulliparous	42	47
Parous	37	42
Pregnancy	8	9
Menopause post-chemotherapy	21	24
Regular cycle post-chemotherapy	71	80
Recovery time for regular cycle (months)	9 (1–54)	
Median time from the end of treatment to pregnancy (months)	50 (35–72)	

Table 3 Characteristics of the eight women with HL who became pregnant

n	Age at diagnosis	Stage	Age at pregnancy	Months from last CHT to pregnancy
1	24	2	27	44
2	24	2	31	92
3	25	2	28	36
4	27	2	36	32
5	28	2	32	56
6	28	2	32	62
7	32	2	34	36
8	31	3	33	40

HL Hodgkin's lymphomas, *CHT* chemotherapy

Discussion

Numerous studies have documented ovarian dysfunction among cancer survivors following cytotoxic chemotherapy [13–15]. Alkylating agents, in particular, produce dose-dependent gonadal toxicity, thought to be due to the depletion of ovarian follicles [15]. Treatment of Hodgkin's lymphoma with MVPP, COPP, or MOPP has been associated with significant risks of ovarian failure, caused by the alkylating agents in these regimens (cyclophosphamide, procarbazine, mechlorethamine) [16, 17].

In addition to its effectiveness in controlling disease, one of the major advantages of ABVD over these prior regimens is the lesser degree of gonadal toxicity, attributable to the lower alkylator dose [18, 19].

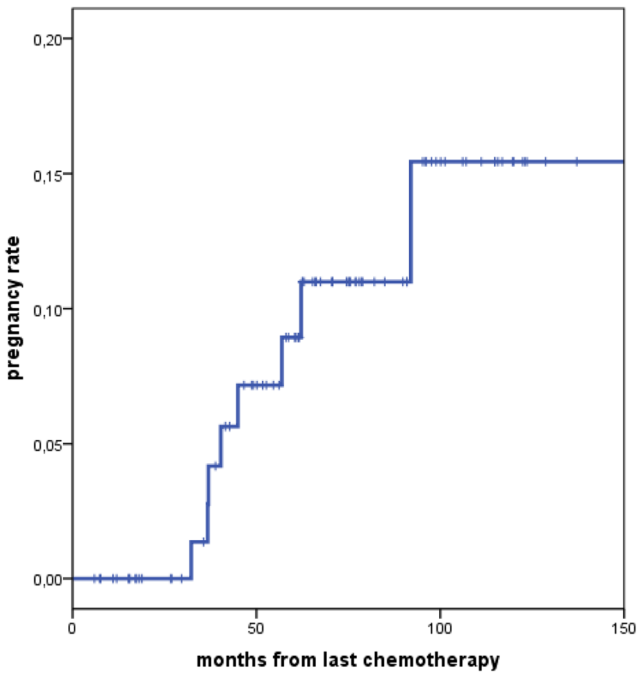

Fig. 1 Pregnancy rate

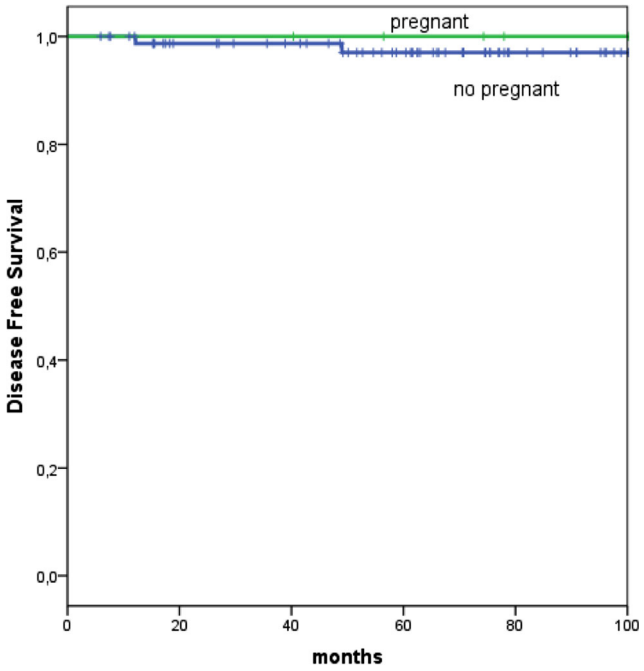

Fig. 2 Disease-free survival

Bonnadonna et al. found that none of 24 women treated with ABVD subsequently experienced amenorrhea [3]. In contrast, Brusamolino et al. found that 16/36 (44%) reported amenorrhea or premature ovarian failure following ABVD, although four had received pelvic RT, and 19 were older than 40 years at the time of treatment [20]. The German Hodgkin's Lymphoma Study Group found that 1/9 evaluable women experienced premature amenorrhea following ABVD [13], and Andre et al. found that all women under 40 retained normal menses after three courses of ABVD [21].

We chose to evaluate women who were recurrence-free 1 year after HL treatment, when the risk of recurrence is low, and the management of late effects of treatment emerges as a clinical concern.

We observed 81% of regular menstrual cycles after treatment, 9% of pregnancies in the entire potential group of 89 patents, and 53% of pregnancies in those patients who tried (15 patients) to become pregnant. Menopause was reached by 21 (24%) women before the age of 50 years. The median time from the end of the therapy to pregnancy was 42 months; the interval between the completion of HL therapy and attempting pregnancy ranged from 32 to 92 months and the cumulative incidence of pregnancy at 70 months was 11% (Fig. 1).

Van der Kaaij et al. found that survivors of HL had fewer children after treatment than did the general population, with personal reasons ranking as the second reason for this; a complete family was the most common reason, and medical reasons were the third most common. They hypothesized that this could reflect a fear of cancer-related complications and an increased cancer risk in offspring, or else pregnancy complications [22].

In our study population, 8/89 women (9%) completed a pregnancy during follow-up and 53% of patients who were attempting pregnancy. Data from Stensheim et al. reported that 32% of the female subjects in their Norwegian cohort diagnosed between 1967 and 2004, aged 16 to 45 years, had a post-diagnosis pregnancy [23].

Besides severity of disease, post-treatment fertility depends on the degree of treatment gonadotoxicity and the patient's age at diagnosis [24]. In a study by Hodgson et al. of 36 female patients with HL who were attempting pregnancy after treatment with ABVD, the percentage of pregnant women within 12 months after diagnosis was 70%, with no significant difference compared with a control group [25].

BEACOPP treatment, especially BEACOPP escalated, is associated with an increased risk of infertility. Furthermore, the oocyte reserve decreases with increasing age [26].

In this study of 89 young women with HL in remission > 1 year, we found no evidence of an increased rate of relapse among women exposed to a recent pregnancy.

This finding is consistent with that of a French study from 1988 comprising 12 patients who were pregnant during treatment for HL or shortly thereafter; the investigators found no evidence that pregnancy influences the course of HL [27].

Weibull et al. reported, in a population-based study which included 449 young women with HL in remission, no evidence of an increased rate of relapse among women exposed to a recent pregnancy [28].

The reproductive pattern before a diagnosis of HL has not been shown to have a negative effect on the incidence or prognosis of HL [28–30]. Moreover, being pregnant at the time of the HL diagnosis does not affect prognosis or survival [31]. One possible explanation for the lack of relapses in women who became pregnant during follow-up could be the so-called healthy-mother effect, meaning that women with less severe disease are more likely to become pregnant after such a diagnosis than other women, and also have a lower risk for relapse [32].

In conclusion, despite the limit of the low number of patients, we found no evidence of an increased rate of relapse among patients with HL who became pregnant during follow-up. The absolute risk for relapse was highest in the first 2 to 3 years after diagnosis. Therefore, women should be advised, if possible, to wait 2 years after the cessation of treatment before becoming pregnant. We recognize, however, that delaying pregnancy is not without complications because chemotherapy can cause early menopause, resulting in involuntary childlessness [27]. In choosing whether to delay pregnancy, older women must weigh up the possibly reduced fertility

against the decreased risk of relapse. Many factors should be considered when deciding about future reproduction. Our findings suggest that the risk of pregnancy-associated relapse does not need to be taken into account in family planning for women in remission from HL.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

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