

Special Article

Fertility in female survivors of Hodgkin's lymphoma

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Currently, Hodgkin's lymphoma is one of the most curable types of cancer. Patients are often young and so the long-term morbidities of treatment have become of increasing concern. Among these, infertility is one of the most challenging consequences for patients in reproductive age. Premature ovarian failure in premenopausal women is a serious long-term sequel of the toxicity of chemotherapy. The main consequence of this syndrome is infertility, but women also present other symptoms related to estrogen deprivation. Different rates of impaired gonadal function are reported, depending on the patient's age, stage of disease, dose and intensity of chemotherapy and the use of radiation therapy. The most established strategy in female infertility is cryopreservation of embryos after in vitro fertilization. Additionally, the use of oral contraceptives or gonadotropin-releasing hormone analogs (GnRH-a) during treatment is under study. This review will provide a general overview of the main studies conducted to evaluate the infertility rate among female Hodgkin's lymphoma survivors and risk factors associated to treatment, different end-point definitions for evaluating fertility and also a brief description of the available strategies for fertility preservation.

Keywords: Hodgkin's lymphoma; Fertility; Survivors

Introduction

Due to the large body of randomized trials conducted by cooperative groups in North America and Europe, the outcome of Hodgkin's lymphoma (HL) has greatly improved over recent decades and HL is today among the most curable malignancies. However, new strategies for further improving HL outcomes in patients should take into account two major concerns: first, a reduction in long-term treatment-related toxicity and second, a decrease in the failure rate for advanced stages.⁽¹⁾

Among the complications, infertility is one of the most challenging consequences for patients in reproductive age. In female survivors, one of major concerns is the risk of premature ovarian failure (POF).⁽²⁾ POF is defined as the premature termination of ovarian function of peripheral origin and is a serious long-term sequel of toxicity. The main consequence of this syndrome is infertility, but women also present symptoms related to estrogen deprivation, such as osteoporosis. Different rates of secondary amenorrhea are reported, depending on the patient's age, stage of disease, dose and intensity of chemotherapy and use of radiation therapy. The most established strategy in female infertility is the cryopreservation of embryos after in vitro fertilization. Also, the use of oral contraceptives or gonadotropin-releasing hormone analogs (GnRH-a) during treatment aimed at preventing secondary ovarian failure is under study.⁽³⁻⁵⁾

This review will provide a general overview of the main studies conducted to evaluate the frequency of infertility among female HL survivors and risk factors associated to treatment, different end-point definitions for evaluating fertility and also, a brief description of the methods of fertilization preservation.

General issues and definitions

The ovaries contain a pool of primordial follicles that decreases during life. At birth, there are about two million follicles, whereas 200 000 remain at puberty and 25 000 at the age of 37 years-old. At the time of menopause there is a pool of fewer than 1000 follicles, when the follicle-stimulating hormone (FSH) levels are insufficient due to declining estrogen levels.⁽⁶⁾

The number of remaining follicles in the ovaries is called the ovarian reserve and represents the woman's current reproductive capacity. The anti-Mullerian hormone (AMH) is produced by early follicles. It has an inhibitory effect on primordial follicle recruitment

Conflict-of-interest disclosure:
 The authors declare no competing financial interest

Submitted: 12/1/2011
 Accepted: 12/4/2011

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DOI: 10.5581/1516-8484.20120014

as well as on the responsiveness of growing follicles to FSH. Its level declines with age and becomes undetectable after menopause.

In premenopausal women, ovarian function is controlled by FSH and luteinizing hormone (LH) produced in the pituitary. FSH activates the granulosa cells of growing ovarian follicles, which proliferate and produce estradiol. This reduces the levels of FSH by feedback inhibition, thus keeping them at low levels. LH at the middle of the cycle induces ovulation following the formation of the luteal body that produces progesterone. The growing follicles also produce inhibin, which prevents an overgrowth of follicles by down regulating FSH.⁽⁷⁾

The main consequence of POF is infertility, but women may also present hot flashes, atrophic vaginitis and osteoporosis. Cancer treatment may induce acute ovarian failure (AOF) shortly after the conclusion of treatment.^(8,9) A proportion of these women resume normal menses within months. Among women who maintain ovarian function after the end of treatment, some may present a premature menopause before the age of 40 years old. In addition to the impact on the quality of life, premature menopause may increase the risk of cardiovascular disease and osteoporosis.⁽⁹⁾

Infertility risk factors

Age

Age and the status of the ovarian reserve before treatment are risk factors for POF in HL. Some studies reported an increase in risk in over 30-year-old women, but this is probably an arbitrary cut-off. Age-related gonadal injury may also be influenced by a natural decline in fertility with increased age. Younger women tolerate higher cumulative doses of chemotherapy before developing amenorrhea and have a greater chance of resuming menses after treatment. On the other hand, older women, who have an already depleted number of follicles at the onset of treatment, are more susceptible to gonadal toxicity.^(3,8,10)

Treatment

While it is well-established that combination chemotherapy causes depletion of the ovarian follicle reserve, the gonadotoxicity of each agent is not easy to establish. Alkylating agents are most often associated with dose-dependent and irreversible gonadal toxicity. The risk of POF is about 50% in young women receiving cyclophosphamide at a mean cumulative dose of 9.3 g. Moreover, there is an 11% increase in the risk of POF with each additional 1.4 g/m² of cumulative procarbazine.^(3,8,10) A summary of the risks of premature menopause of each drug is shown in Table 1.

Table 1 - Risk of premature menopause in women treated for Hodgkin's lymphoma using different agents

Agent	Hazard ratio (95% CI)*
Vincristine	1.6 (0.7-03.6)
Vinblastine	0.5 (0.2-01.4)
Doxorubicin	0.4 (0.2-01.1)
Bleomycin	1.0 (0.4-02.4)
Procarbazine	8.1 (2.0-32.8)
Cyclophosphamide	3.5 (2.0-05.9)
Dacarbazine	0.3 (0.1-01.5)
Lomustine	1.6 (0.7-03.6)
Chlorambucil	2.0 (0.8-04.7)
Carmustine	0.7 (0.1-03.7)
Ifosfamide	1.3 (0.2-10.3)

Adapted from De Bruin et al.⁽⁸⁾

95% CI: 95% confidence interval

*compared with women who were treated with radiotherapy only, provided the ovaries were not localized in the radiation fields

Currently, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) are the most frequently used regimens for treating HL.⁽¹⁾ In general, ABVD is not associated with a greater risk of premature menopause. Hodgson et al. reported the results of a case-control study of thirty-six female HL survivors who had attempted pregnancy and found no evidence of significant impairment in fertility compared to controls.⁽¹¹⁾ The German Hodgkin Study Group (GHS) analyzed the menstrual status after HL treatment of 405 patients.⁽¹⁰⁾ They found a proportion of 51.4% of the women who had received eight cycles of escalated BEACOPP had permanent amenorrhea. The escalated regimen produced a higher rate of amenorrhea than standard BEACOPP.

In a large cohort of 518 female HL survivors, after a median follow-up of 9.4 years, 97 women reached menopause before the age of 40 years.⁽⁸⁾ Chemotherapy was associated with a 12.3-fold increase in premature menopause, when compared to radiotherapy alone. Also, abdominal or pelvic radiation increases the risk of POF.

The literature concerning the risks of infertility after hematopoietic cell transplantation (HCT) is scarce. Some studies have pointed out that the risk with allogeneic stem-cell transplantation is the highest, especially after total body irradiation (TBI). However, a report from the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) revealed the occurrence of 83 pregnancies in female HCT recipients. The series included recipients of autologous HCT, myeloablative allogeneic HCT and non-myeloablative allogeneic HCT.⁽¹²⁾

A summary of the main studies about risk factors of impaired gonadal function in female HL patients is presented in Table 2.

Table 2 - Treatment-related risk of infertility for patients with Hodgkin's lymphoma

Study	n	Disease	Follow-up years	End-point	Treatment	Results (%)	Risks factors
Behringer et al. ⁽¹⁰⁾	405	HL	3.2	Amenorrhea	RT	6.3	Alkylating agent, age, disease stage, no oral contraception
					ABVD	3.9	
					4 COPP/ABVD	37.5	
					8 BEACOPP	22.6	
					8 BEACOPP escalated	51.4	
Decanter et al. ⁽¹³⁾	30	HL and NHL	1	AMH dosage	ABVD Others including alkylating agents	Normal decreased	
Hodgson et al. ⁽¹¹⁾	36	HL	1	Parenthood	ABVD	Same as controls	
Brusamolino et al. ⁽¹⁴⁾	67	HL	10	Amenorrhea and parenthood	ABVD	Fertility preserved	
Franchi-Rezgui et al. ⁽¹⁵⁾	84	HL and NHL	8	Parenthood	Many regimens with alkylating agents	37 preserved fertility	Dose of alkylating agent and age
Kiserud et al. ⁽¹⁶⁾	91	HL	10	Parenthood	Non-alkylating	55	Dose of alkylating agent and age
					Alkylating (limited number of cycles)	21	
					High-dose chemotherapy and alkylating regimens > 4 cycles	27	
De Bruin et al. ⁽⁸⁾	518	HL	9.4	Premature menopause	Radiotherapy, MOPP or MOPP/ABV ABVD/EBVP		Highest associations of premature menopause with alkylating agents

Adapted from Harel et al.⁽⁴⁾

HL: Hodgkin's lymphoma; NHL: Non-Hodgkin lymphoma; ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; COPP/ABVD: Cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; EBVP: Epirubicin, bleomycin, vinblastine, dacarbazine; AMH: Anti-Mullerian hormone; RT: Radiation therapy

Evaluation of fertility

Infertility is defined as the failure to conceive after one year of regular intercourses without taking contraceptive measures. Infertility secondary to cancer treatment may be transient, permanent or delayed.⁽⁵⁾

The diagnosis of POF is based on clinical and laboratory evidence. Ovarian reserve tests (ORT) include ultrasound and serum biomarkers.^(4,8,17)

Clinical evidence is based on the presence or absence of menstrual cycles. After treatment, the recovery of normal menstrual cycles does not warrant normal fertility, but amenorrhea is the strongest predictor of infertility. Also, the presence of transient amenorrhea after treatment is a risk factor for subsequent infertility.^(4,17)

Laboratory evidence includes determining the serum levels of FSH, AMH and inhibin B. Usually, levels of FSH are elevated in cases of impaired fertility, but normal levels do not exclude impaired ovarian function. The AMH is undetectable after menopause. Also, the level of inhibin, which is secreted by the follicles, decreases with age.

Moreover, transvaginal ultrasound has been evaluated in the diagnosis of POF. The antral follicle count (AFC) and

also the ovarian volume are useful parameters associated with ovarian reserve and fertility.⁽¹⁸⁾

It is also known that patients with Hodgkin's lymphoma may face infertility at the time of diagnosis, that is, before treatment. Data come mostly from studies performed in men, but it is possible that similar mechanisms operate in women. Some studies evaluating semen quality before treatment showed that most patients had azoospermia or dyspermia. The underlying mechanism of infertility in HL patients is still unknown. Possible factors are damage to the germinal epithelium and disorders of the hypothalamic-hypophysial axis as well as the impact of cytokines on spermatogenesis.⁽¹⁹⁾

Fertility preservation strategies

Assisted reproduction

The most established strategy for female infertility is assisted reproduction (embryo and oocyte cryopreservation). However, this approach has some limitations. Only pubertal patients and patients with a long-term partner can benefit from this procedure. Also, patients presenting an urgent medical complication cannot wait for the delay imposed by

the procedure, since the process usually requires a delay of one month before starting chemotherapy. Alternatives under study are fertilization of oocytes by intracytoplasmic sperm injection and oocyte vitrification.^(4,20)

Cryopreservation of ovarian tissue

This represents an investigational method offered to pre-pubertal and pubertal females. The general principle is to remove the ovary or obtain an ovarian cortex biopsy and freeze the primordial follicles using established protocols. Nevertheless, only 12 full-term pregnancies using this method have been reported so far, and among them only 4 in patients with HL. So, the results are still uncertain.^(4,21-23)

Pharmacological methods – Gonadotropin-releasing hormone analogues (GnRH) and oral contraceptives

There are many suggested mechanisms of protection against gonadotoxicity by GnRH-a.⁽²⁴⁾ The first is the creation of a hormonal milieu similar to the pre-pubertal state. It has been hypothesized that chemotherapy induces an accelerated rate of follicular destruction with subsequent decreases in the production of estradiol and inhibin resulting in increases in FSH production. This increase in FSH causes

enhanced recruitment of follicles and subsequent destruction. The administration of GnRH or oral contraceptives may prevent the increased levels of FSH by inducing pituitary desensitization, thus protecting the follicles. Another possible mechanism is decreased utero-ovarian perfusion. It has been speculated that this decrease in perfusion could reduce the exposure of ovaries to chemotherapeutic agents. Finally, a potential direct effect on GnRH receptors has been proposed.

Several studies have been published to establish the role of GnRH-a and oral contraceptives in preserving fertility in female cancer patients. However, the literature is still controversial.^(24,25) In a retrospective study, GnRH-a allowed the recovery of menses in 92% of patients and all 13 patients that attempted pregnancy conceived.⁽³⁾ In another prospective study, 97% of patients taking GnRH-a resumed ovulation and regular menses compared with 63% control subjects.⁽²⁶⁾ On the other hand, a randomized prospective trial aimed to compare oral contraceptives and GnRH-a in female HL patients treated with escalated BEACOPP was recently closed because neither arm protected ovarian function as measured by AMH levels.⁽²⁷⁾ Furthermore, the authors that are against the recommendation of the use of GnRH for young female patients outside clinical trials argue that: (i) most of the data came from retrospective studies with limited numbers of patients, (ii) there is a lack of prospective, randomized clinical trials, (iii) there is a lack of biological

Table 3 - Summary of studies in lymphoma patients evaluating the role of GnRH analogue in preserving female fertility

Study	Study group	Design	n	Regimen	Disease	POF (%)	Comments
Falorio et al. ⁽³⁾	GnRH-a	Retrospective	61	ABVD & alkylating containing regimens	HL	-	Recovery of normal menses in 92% regardless of front-line chemotherapy regimens
Waxman et al. ⁽²⁸⁾	GnRH-a	Prospective, randomized	8	MVPP	LNH	75	Small sample size
	Control		10			80	
Blumenfeld et al. ⁽²⁹⁾	GnRH-a	Prospective, historical control group	16	Alkylating & non-alkylating containing regimens)	LNH	6	Longer follow-up in controls
	Control		18			61	
Dann et al. ⁽³⁰⁾	GnRH-a	Prospective, nonrandomized	7	Mega-CHOP	LNH	0	Small sample size, no statistical analysis
	Control		6			16	
Behringer et al. ⁽²⁷⁾	GnRH-a OC	Prospective randomized		Escalated BEACOPP	HL	-	This study was closed prematurely. Neither arm was able to ensure protection regarding FSH-based ovarian protection rates.
Blumenfeld et al. ⁽²⁶⁾	GnRH-a	Prospective study with historical controls	65	ABVD & procarbazine-containing regimens	HL	3	Not randomized. Effects probably only in younger patients < 37 years old
	Control		46			63	
Huser et al. ⁽³¹⁾	GnRH-a	Prospective case-control study	72	Alkylating & non-alkylating containing regimens)	HL	71	Reduction of ovarian failure risk in women with HL treated with less aggressive regimens plus a GnRH analogue
	Control		45			20	

Adapted from Blumenfeld Z et al. and Oktay K et al.^(24,25)

ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; MVPP: Mechlorethamine, vinblastine, procarbazine and prednisone; Mega-CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; GnRH-a: Gonadotropin-releasing hormone analogs; OC: Oral contraceptives; HL: Hodgkin's lymphoma; NHL: Non-Hodgkin lymphoma

plausibility for protection by GnRH and also, (iv) there are concerns about the safety of the procedure.⁽²⁵⁾ On the other hand, some other authors consider that the published clinical studies provide some evidence that GnRH-a reduces gonadotoxicity and GnRH-a can even reduce some chemotherapy-induced complications, such as severe menometrorrhagia. In 2011, the results of a randomized trial, PROMISE-GIM6, showed that the use of triptorelin during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of early chemotherapy-induced menopause. A summary of the main studies is presented in Table 3.

Impairment of reproductive function can be a significant late effect of cancer treatment, mainly for young female patients. Understanding the major risk factors and the role of alternative strategies such as the use of GnRH-a or oral contraceptives during treatment will help prevent gonadal damage. The benefits and risks of each treatment regimen must be discussed individually, mainly with female patients older than 30 years old and those receiving alkylating-containing regimens. Also, if available, patients should be offered assisted reproductive consultations. Finally, a careful assessment of the ovarian function before treatment should be performed in all circumstances and the collection of such information should be encouraged when planning prospective clinical trials as well as lymphoma registries.

Acknowledgments

Financial support provided by the Associazione Angela Serra per la Ricerca sul Cancro, Modena, Italy and FAPERJ (*Fundação de Amparo à Pesquisa do Rio de Janeiro*)

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