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Impact of Ovarian Transposition before Pelvic Irradiation on Ovarian Function among Long-term Survivors of Childhood Hodgkin Lymphoma: A Report from the St. Jude Lifetime Cohort Study

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Abstract

Background—We reviewed the effect of ovarian transposition (OT) on ovarian function among long-term survivors of childhood Hodgkin lymphoma (HL) treated with pelvic radiotherapy.

Procedure—Female participants (age 18+ years) with HL in the St. Jude Lifetime Cohort Study (SJLIFE) were clinically evaluated for premature ovarian insufficiency (POI) 10 or more years after pelvic radiotherapy. Reproductive history including age at menopause and pregnancy/live births was available on all patients.

Results—Of 127 eligible females with HL, 90 (80%) participated in SJLIFE including 49 who underwent OT before pelvic radiotherapy. Median age at SJLIFE evaluation was 38 years (range 25-60). In a multiple regression adjusted for age at diagnosis, pelvic radiotherapy doses > 1,500 cGy (HR=25.2, 95% CI=3.1 to 207.3; p=0.0027) and cumulative cyclophosphamide equivalent

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Conflict of interest Statement

None of the authors has a conflict of interest to declare.

doses of alkylating agents > 12,000 mg/m^2 (HR=11.2, 95% CI=3.4 to 36.8; p<0.0001) were significantly associated with POI. There was no significant association between OT and occurrence of POI (HR=0.6, 95% CI=0.2 to 1.9; p=0.41).

Conclusions—OT did not appear to modify risk of POI in this historic cohort of long-term survivors of HL treated with gonadotoxic therapy. Modern fertility preservation modalities such as mature oocyte cryopreservation should be offered to at-risk patients whenever feasible.

Keywords

late effects; Hodgkin lymphoma; premature ovarian insufficiency; ovarian transposition

INTRODUCTION

Premature ovarian insufficiency (POI) is defined by the absence or interruption of spontaneous pubertal development in children and adolescents or by the onset of menopause before age 40 as a result of primary gonadal failure [1]. Up to 11% of female survivors of childhood cancer experience POI [2–4]. Lower ovarian reserve in young adulthood has been observed in women treated with chemotherapy and radiation therapy during childhood for Hodgkin lymphoma (HL) [5,6]. Exposure to high dose alkylating agents, quantified by cyclophosphamide equivalent dose (CED) ≥8,000 mg/m^2 has been associated with POI further highlighting the ovarian toxicity of these agents [2]. Pelvic radiotherapy can also cause irreversible ovarian damage and lead to infertility and other long-term health concerns such as decreased bone mineral density and frail health [2]. The estimated dose of radiation at which half of the follicles are lost in humans is 4-6 Gy in adults and 10-20 Gy in children [7–9]. Older age at radiotherapy has been associated with a higher risk of POI, likely because of the natural decline of ovarian reserve with age [3].

Ovarian transposition (OT) was proposed in 1958 as a means to preserve fertility in girls with tumors requiring pelvic irradiation [10]. This procedure involves relocation of the ovaries out of the irradiation field to minimize exposure of the ovaries to radiation, thereby preserving ovarian function [11]. Studies reporting on ovarian function in childhood cancer survivors who underwent OT have generally been limited and confined to studies with small sample size and short follow-up.

The aim of this study was to evaluate the risk of POI and describe patterns of pregnancy and live births in a cohort of long-term female survivors of HL exposed to pelvic radiotherapy including a subset who underwent OT before radiation.

MATERIAL AND METHODS

Study participants

Eligibility criteria for inclusion included: (1) females treated with pelvic radiotherapy during childhood for HL at St. Jude Children's Research Hospital (SJCRH); (2) survival of >10 years from diagnosis; and (3) attained age ≥18 years of age at follow-up [12,13]. Eligible survivors underwent a clinical assessment on-campus and completed a series of questionnaires pertaining to reproductive health prior to June 30, 2015. Survivors with a

history of surgical menopause or bilateral oophorectomy before age 40 years, or hypothalamic or pituitary area irradiation were excluded. The study was approved by the institutional review board and the participants provided written informed consent prior to assessment.

Study outcomes

Premature ovarian insufficiency was defined as absence of menses five years post cancer diagnosis, or loss of spontaneous menses prior to 40 years of age with laboratory or historic evidence of primary (ovarian) origin. The diagnosis of POI was based on the medical history provided by the patients in regards to puberty, menarche, menstrual cycles, pregnancies, childbirth, use of hormonal therapies including contraception and timing of menopause, and supplemented by clinical and laboratory data from the SJLIFE evaluation [2]. In the absence of treatment with oral contraceptive pills or sex-hormone replacement therapy (HRT) at the time of SJLIFE participation, individuals < 40 years old experiencing amenorrhea > 6 months and having plasma estradiol levels < 17 pg/mL coinciding with FSH ≥30 IU/L were considered to have POI. The diagnosis of POI was based on historical medical information only in participants treated with oral contraceptives or HRT [2]. Additional information on pregnancy and live births was obtained from questionnaires.

Study variables

Exposure to alkylating agents was quantified using the validated cyclophosphamide equivalent dose (CED) [14]. History of OT was abstracted from the medical record. The technique used in SJCRH involved transposition of the ovaries to a midline position behind the uterus by either an open procedure or laparoscopy.

Statistical analyses

Descriptive statistics were used to characterize participants and non-participants, as well as those who underwent OT and those who did not. Characteristics were compared between groups with Fisher’s exact test or Wilcoxon rank sum test as appropriate. Cox proportional hazard regression was used to examine associations between treatments (OT, CED and pelvic radiation) and POI after adjusting for age at diagnosis. Time-to-event analysis was used to compare pregnancies and live birth deliveries between survivors with and without OT, with POI considered a competing risk. Analyses were completed in SAS version 9.4 (Cary, NC) and R 3.4.2.

RESULTS

Characteristics of study participants

Of 127 eligible females with HL, 90 (80%) participated in SJLIFE including 49 who underwent OT before pelvic radiotherapy (Figure 1). Participants did not differ from non-participants by race/ethnicity, age at diagnosis of HL, age at OT, pelvic radiation dose, CED, nitrogen mustard dose or procarbazine dose (Table 1). However, participants who underwent OT were younger when diagnosed with HL (P=0.04), received significantly higher doses of pelvic radiation (P<0.0001) and more alkylating agents (P=0.04) compared to survivors who did not undergo OT (Table 2). Among survivors who underwent an OT, an open surgical

technique was used in 48 (98%) and a laparoscopic approach in 1 (2%). Bilateral midline OT was performed in all cases.

Risk factors associated with POI

In multivariable models, there was no significant association between OT and occurrence of POI (hazard ratio [HR]=0.6, 95% confidence interval [CI]=0.2 to 1.9; p=0.41). However, pelvic radiotherapy doses > 1,500 cGy (HR=25.2, 95% CI=3.1 to 207.3; p=0.0027) and exposure to alkylating agents at cumulative CED > 12,000 mg/m^2 (HR=11.2, 95% CI=3.4 to 36.8; p<0.0001) were associated with an increased risk of POI (Table 3). A multivariable sub-analysis was conducted to examine associations between OT, pelvic radiation dose and POI among survivors who received lower CED (<12000 mg/m2). After adjusting for age at diagnosis, there was a significant association between POI and pelvic radiation dose (HR=17.8, 95% CI=2.3 to 136.5; P=0.0057) but not with OT (HR=1.1, 95% CI=0.5 to 2.7; P=0.8052) (Table 4).

Ovarian function between survivors who did or did not undergo OT

The median age at POI for survivor participants with or without OT was not significantly different (22.7 [range, 15.3-38.2] vs. 17.9 [range, 15.5-35.0] years, p=0.2629) (Table 2). Among the 49 survivors who had OT, 30 (61%) reported at least one pregnancy, and for those who reported pregnancy, 27 (90%) reported a live birth delivery at least once. The probability of a first pregnancy or a live birth before age 40 were did not differ between OT and non-OT groups (P=0.1360 and P=0.4970, respectively) (Figure 2).

DISCUSSION

Our study provides long-term follow-up data on the effect of OT on ovarian outcomes (POI, pregnancy and live births) in a cohort of clinically assessed HL survivors treated with pelvic radiotherapy. The study is unique in its ability to assess the effect of OT in relation to gonadotoxic therapy that may impact ovarian function, and in the extended duration of follow-up, which is among the longest reported to date. This study is timely given the increased availability of modern fertility preservation techniques, and the need for data to assist childhood cancer survivors and their families to make the best decisions possible in regards to future fertility and family planning [15].

Prior studies have reported variable success rates of OT performed at staging laparotomy for female HL patients in regards to preservation of ovarian function, ranging from 0% to 66% [16–21]. In this study, OT did not appear to modify the long-term risk of POI among female survivors of HL. However, it is important to note that OT was performed in a higher proportion of individuals treated with the highest doses of pelvic irradiation and exposure to higher doses of alkylating agents, which could have been a source of substantial bias. In addition, the effects of gonadotoxic treatments may have overwhelmed potential long-term gains from OT. Notably, age at first pregnancy and pregnancy/live birth history were not significantly different between patients with or without OT, despite of the fact that survivors with OT were treated with higher dose of pelvic irradiation.

Our study indicates that OT may not prevent ovarian injury with use of combined modality therapy including pelvic radiotherapy doses > 1,500 cGy and alkylating agents exceeding a CED > 12,000 mg/m^2. Prior studies with smaller numbers of patients, and shorter follow-up, have observed variable results in regards to preservation of ovarian function following OT and pelvic irradiation. Pregnancies have been reported in women who had OT, but small cohort sizes precluded inclusion of patient and treatment factors that may confound or modify the association between OT and preserved ovarian function. Ray et al. [17] reported preservation of ovarian function in 59% of 22 patients who underwent OT, one of whom gave birth to a normal baby girl. Le Floch et al. [18] reported on nine patients who underwent OT prior to pelvic radiation therapy and became pregnant; six patients had given birth to eight babies. An additional two patients had therapeutic abortions and one a spontaneous abortion. Thomas et al. [19] reported reproductive and endocrine function in 22 women with HL who had bilateral mid-line OTs performed at staging laparotomy. OT was only partially successful, preserving fertility in 30% of the patients. Terenziani et al. [20] reported reproductive patterns in 11 HL patients who underwent open bilateral OT at a median age of 13 years. Fourteen pregnancies were recorded among these 11 women, with 12 live births (1 pair of twins) and 3 miscarriages. The median age at the time of first pregnancy was 31 years, and the median time since OT was 14 years. In this series, only 4 patients received both chemotherapy and radiation. Five patients received radiation exclusively, and 2 patients did not receive radiation. In our long-term follow-up study, 68% of study participants reported at least one pregnancy, with no significant difference between OT (61%) and non-OT (76%) groups. In a meta-analysis of 1189 premenopausal women with cancer requiring primary or postoperative radiotherapy (median age of 32 years), ovarian function following OT was preserved in 70% of women [21]. However, patients were only followed for a median of four years (range, 2-16), and the study only included women exposed to pelvic radiation. The median age at OT in our study was 15 years (range, 4-24), and the median age at evaluation was 38 years (range 25-60). Our findings highlight the importance of long-term follow-up to better define the role of OT in delaying the onset of menopause in cancer survivors.

The transposition of ovaries during surgical staging for HL was first reported in 1970 by Stanford investigators [22]. This procedure can be performed by laparotomy, laparoscopy or percutaneous needle transposition. All but one of our patients underwent an open procedure, therefore we were unable to evaluate the theoretical benefit of a less invasive surgical approach. Complications associated with OT include increased ovarian cyst formation, postoperative adhesions, chronic pelvic pain, migration of the ovaries back to their native position, damaged or dysfunctional fallopian tubes and spread of unnoticed metastatic disease within the ovaries. Also, OT does not protect the ovaries from the effects of gonadotoxic chemotherapy. For all these reasons, treatment with systemic gonadotoxic drugs should be taken into consideration when assessing the risk of the procedure.

There are several limitations of this study. First, the small number of patients with OT limited our ability to adjust for confounding variables in analysis. Our non-inclusion of etiologies other than HL limits our ability to relate our findings to the rest of the literature as treatment exposures vary by type and stage of cancer. Second, because a substantially higher percentage of our patients exposed to high dose irradiation were treated with OT, our ability

to detect the protective effect of OT for those with lower dose exposure may have been limited. Third, techniques for radiation delivery have changed from 1962 to 2005. Data from older female survivors may not apply to girls treated today. In addition, this study does not incorporate dosimetry calculations based on the position of the ovaries after they were moved. Therefore, the findings do not allow the quantification of the radiation dose reduction brought about by the procedure and that this is subject to variations depending on the individual's anatomy and the success of the procedure itself. Fourth, data pertaining to pregnancy and live birth history depended on accurate completion of relevant questionnaires. Self-report data is always subject to recall bias, although maternal recall of reproductive history is generally accurate [23]. Fifth, the observed results in survivors who underwent OT may be a result of an operative failure or procedural complication that was not recorded. This study does not address potentially pre-existing conditions of the ovary and that may have already affected follicular reserve, such as unilateral oophorectomy. Further discussion of operative complications is warranted. Finally, the cross-sectional design of this study poises specific challenges in reporting the outcomes of interest given that a subset of patients may still go on to experience either POI or pregnancies with further follow-up.

In summary, OT did not appear to modify the long-term risk of POI and the pregnancy/live birth events in this historic cohort of long-term survivors of HL treated with combined pelvic radiation and alkylating agents. Modern fertility preservation modalities such as mature oocyte cryopreservation should be offered to at-risk patients whenever feasible.

Acknowledgments

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ABBREVIATION KEY

CED	Cyclophosphamide Equivalent Dose
CI	Confidence Interval
FSH	Follicle Stimulating Hormone
HL	hodgkin lymphoma
hr	hazard ratio
hrt	sex hormone replacement Therapy
ot	ovarian transposition
poi	Premature Ovarian Insufficiency
sjlife	St. Jude Lifetime Cohort Study
Sjcrh	St. Jude Children's Research Hospital

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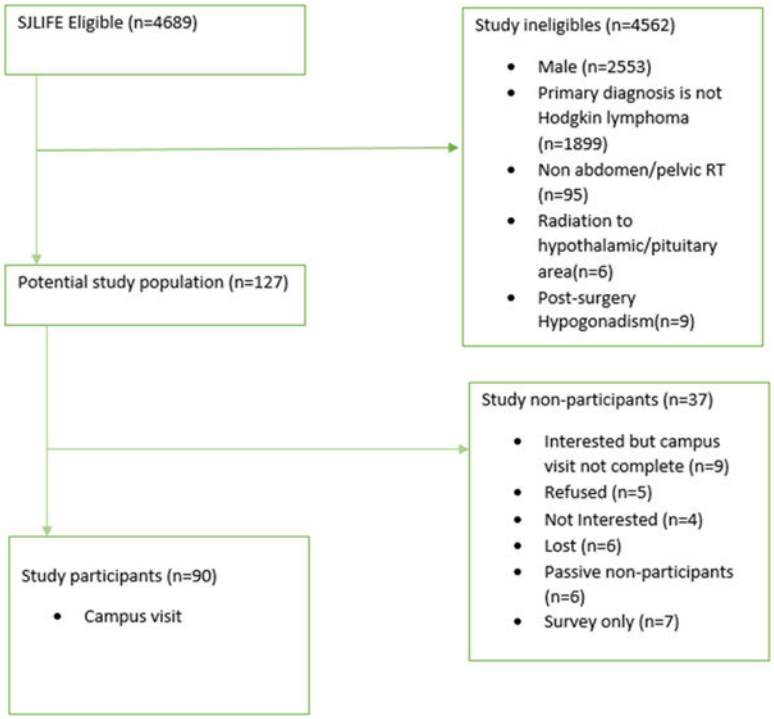

Figure 1.
Consort diagram

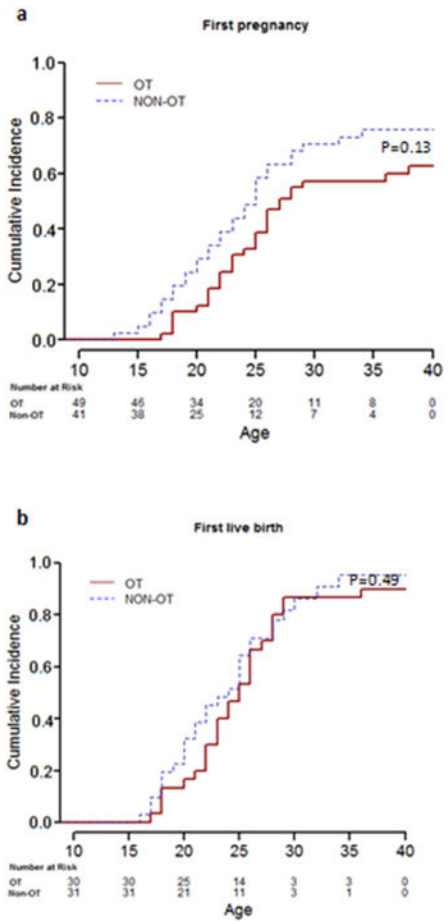

Figure 2.

Cumulative incidence plot for the probability of first pregnancy (2a) and live birth over time (2b)

Table 1

Comparison of presenting features and treatments between study participants and non-participants

	Participants (N=90)	Non-Participants (N=37)	P value
Age at diagnosis, Median (range)	16 (4-22)	15 (6-20)	0.3079
Age at Ovarian transposition, Median (range)	15 (4-24)	14.5 (7-22)	0.9364
Race/Ethnicity (N, %)			0.2277
White	77 (85.6)	35 (94.6)	
Non-white	13 (14.4)	2 (5.4)	
Ovarian transposition (N, %)			0.2804
Yes	49 (54.4)	24 (64.9)	
No	41 (45.6)	13 (35.1)	
Pelvic radiation dose (N, %), cGy			0.2932
≤ 1500	32 (36.8)	9 (25.0)	
> 1500	55 (63.2)	27 (75.0)	
Alkylating Agent Cyclophosphamide Equivalent Dose (N, %), mg/m^2			0.5815
0 to <= 8000	45 (51.7)	21 (58.3)	
8000 to <= 12000	18 (20.7)	7 (19.4)	
12000 to <= 20000	20 (23.0)	5 (13.9)	
> 20000	4 (4.6)	3 (8.3)	
Median (range)	8818.2 (1800.0-28980.0)	8034.4 (2339.0-31625.9)	
Nitrogen mustard (N, %), mg/m^2	3 (3.3)	2 (5.4)	
Median (range)	18.4 (18.1-36.7)	20.7 (17.5-23.9)	0.7728
Procarbazine (N, %), mg/m^2	65	31	
Median (range)	4433.3 (857.1-15633.3)	4114.3 (714.3-17710.5)	0.6779

Table 2

Comparison of presenting features and treatments between survivor participants with or without ovarian transposition

	Ovarian transposition (N=49)	Non-ovarian transposition (N=41)	P Value
Age at diagnosis, Median (range)	15 (4-19)	16 (6-22)	0.0417
Age at Questionnaire, Median (range)	38 (25-51)	39 (26-60)	0.9353
Age at primary ovarian insufficiency, Median (range)	22.7 (15.3-38.2)	17.9 (15.5-35.0)	0.2629
Race			0.9626
White	42 (85.7)	35 (85.4)	
Non-white	7 (14.3)	6 (14.6)	
Alkylating Agent Cyclophosphamide Equivalent Dose (N, %), mg/m^2			0.0445
0 to <= 8000	19 (39.6)	26 (66.7)	
8000 to <= 12000	12 (25.0)	6 (15.4)	
12000 to <= 20000	13 (27.1)	7 (18.0)	
> 20000	4 (8.3)	0 (0.0)	
Median (range)	10151.7 (1806.2-28980.0)	7434.6 (1800.0-16486.8)	
Pelvic radiation dose (N, %), cGy			<.0001
≤ 1500	9 (18.4)	23 (60.5)	
> 1500	40 (81.6)	15 (39.5)	
Pregnancy			0.1459
Yes	30 (61.2)	31 (75.6)	
No	19 (38.8)	10 (24.4)	
Age at first pregnancy, Median (range)	23.5 (17.0-38.0)	22.0 (13.0-34.0)	0.1693
Live birth delivery *			0.9663
Yes	27 (90.0)	28 (90.3)	
No	3 (10.0)	3 (9.7)	
Age at first live birth delivery, Median (range)	24.0 (17.0-36.0)	22.5 (16.0-34.0)	0.3272

* Analysis for the live birth delivery was based on patients who have reported pregnancy (N=61, 30 in OT and 31 in non-OT group)

Table 3

Multiple regression to investigate the association between OT and POI

		Hazard Ratio (95% CI)	P
Alkylating agent cyclophosphamide equivalent dose, mg/m2	<= 8000	Ref.	
	8001-12000	3.3 (0.7, 16.0)	0.1461
	12001-2000	11.2 (3.4, 36.8)	<0.0001
	>20000	36.9 (5.2, 260.5)	0.0003
Ovarian transposition	No	Ref.	
	Yes	0.6 (0.2, 1.9)	0.4069
Pelvic radiotherapy dose, cGy	≤ 1500	Ref.	
	>1500	25.2 (3.1, 207.3)	0.0027

Table 4

Multiple regression to investigate the association between OT and POI among patients who had low dose CED (<=12000 mg/m2)

		Hazard Ratio (95% CI)	P
Ovarian transposition	No	Ref.	
	Yes	1.1 (0.5, 2.7)	0.8052
Pelvic radiotherapy dose, cGy	≤ 1500	Ref.	
	>1500	17.8 (2.3, 136.5)	0.0057