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Premature ovarian insufficiency in pediatric cancer patients: a 10 year Rady Children's Hospital experience

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Abstract

Objectives: To highlight the occurrence of premature ovarian insufficiency in pediatric cancer patients and determine which patient characteristics or treatment modalities are associated with ovarian failure and recovery.
Methods: Between August 2011–August 2021, 36 of 2,661 patients with cancer were identified to have subsequent ovarian failure. Data collected included cancer type, diagnosis age, types of chemotherapy, bone marrow transplant or radiation treatment, peak follicle-stimulating hormone (FSH), peak anti-Mullerian hormone (AMH), gonadotropin releasing hormone agonist (GnRHa) treatment, type of hormone replacement therapy, and if ovarian function recovery occurred.
Results: The most common cancer type identified was ALL. The mean age of diagnosis was 8.5±4.3 years and mean age of peak FSH value was 12.6±2.8 years. Most patients (97.2 %) were treated with alkylating agents and 72.2 % received radiation. Most patients (72.2 %) received hormone therapy, and 15.8 % of patients received GnRHa Lupron. Ten patients (27.8 %) had ovarian function recovery. Diagnosis age and treatment type were recovery predictors in multivariate regression modeling. Each year older in age was associated with a 30 % decrease in odds of recovery (OR: 0.7, CI: 0.5–0.95, p=0.035), and alkylating agent treatment without transplant was associated with a 3-fold increase in odds of recovery (OR: 3, CI: 2.7–564, p=0.007).
Conclusions: This retrospective review demonstrates that POI can occur in pediatric cancer survivors, emphasizing the importance of educating patients on potential long-term effects of cancer treatment and importance of routine surveillance. This study confirmed that recovery of ovarian function is possible, especially when diagnosed at a younger age, making continued monitoring essential.

Keywords: pediatric cancer survivors; premature ovarian insufficiency; recovery of ovarian function

Introduction

The five-year survival rate for pediatric cancers now exceeds 85 %, necessitating improved understanding of the potential late effects and comorbidities that may result from these diseases and their treatment [1]. Primary (or premature) ovarian insufficiency (POI), a type of ovarian dysfunction that can present with primary amenorrhea, is one such potential late effect for these survivors. The diagnostic criteria for this condition include females younger than 40 years of age, lack of menses for four months or longer, and two elevated values of follicle-stimulating hormone (FSH) in the menopausal range [2]. In pediatric cancer survivors, the incidence of POI is thought to fall between 2 and 8 % [3, 4], as compared to an estimated incidence of 0.4 % in the general population (for women less than 36 years of age) [5]. Given that POI is associated with increased risk for osteoporosis, cardiovascular disease, infertility, and all-cause mortality [6], a detailed exploration of the contributory factors, prevention measures, treatment methods, and outcomes for this condition is essential to inform best clinical practice.

Alkylating agents are among the most common chemotherapeutics [7], and it is well established that these agents can induce gonadotoxicity by promoting cell death and accelerating activation of primordial follicles [7]. Radiation therapy (including but not limited to pelvic radiation), often used in conjunction with chemotherapy, is another known cause of POI, and doses of 10–30 Gy have been demonstrated to acutely impact ovarian function in a majority of patients treated [8]. Unsurprisingly, increasing dose of radiation is associated with a greater risk for ovarian failure [8].

Miranda Robinson and Leo Meller contributed equally to this work and share first authorship.

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Accordingly, both alkylating agent exposure and radiation therapy have been demonstrated to correlate with increased POI risk in childhood cancer survivors [3].

General recommendations have been proposed regarding surveillance for POI in pediatric cancer survivors exposed to alkylating agents and/or radiation to the ovaries [2]. These recommendations include monitoring FSH and estradiol in pre-pubertal children with improper puberty progression and in post-pubertal children with menstrual cycle dysfunction [2]. Once POI has been diagnosed, referral to gynecology or endocrinology is recommended where treatment with sex steroid replacement therapy, most preferably transdermal estrogen (due to its bone and cardiovascular health benefits), can be initiated [2]. Despite this, the natural history of non-autoimmune POI is poorly characterized and clinical trials evaluating the efficacy of these therapies are lacking [9]. This retrospective study aims to address these shortcomings by identifying the patient characteristics and treatment modalities associated with ovarian failure and subsequent recovery in a population of childhood cancer survivors with POI.

Methods

This single center, retrospective chart review spanned a 10-year period between August 2011 and August 2021 at Rady Children's Hospital San Diego. During this time frame, 38 of 2,661 pediatric patients with cancer were identified to have subsequently developed ovarian failure, as defined by FSH elevation above age and Tanner-stage-adjusted lab reference values and all patients in the study had an FSH value of 20 IU/L or higher. Two individuals were excluded for missing data, yielding 36 patients for analysis. Data collected included age at diagnosis, type of cancer, chemotherapeutics used in treatment, use of bone marrow transplant, use of radiation, location of radiation, use of gonadotropin releasing hormone agonist (GnRHa), use of hormone replacement therapy, type of hormone replacement therapy, peak FSH value and age when this occurred, peak anti-Mullerian hormone (AMH) value, and whether there was recovery of ovarian function. Type of cancer was classified as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), brain/central nervous system (CNS), solid tumor, or other; chemotherapy regimen was classified as alkylating agent (including platinum analogs), combination therapy (alkylating agent + bone marrow/stem cell transplant), or other; radiation location was classified as total body irradiation (TBI), pelvic, or other; and hormone replacement therapy type was classified as oral, transdermal, or combination (oral + transdermal). This study was determined to not require IRB review by the E-QUAL Committee at Rady Children's Hospital San Diego.

Statistical analysis

Categorical data are presented as count and percentage while continuous data are summarized as median (IQR). Fisher's exact test was implemented for categorical comparisons due to small sample size and expected cell counts less than 5. To account for non-normality in the continuous data, Mann-Whitney U tests were implemented to assess statistical differences. Univariate logistic regression models were fit to assess the univariate relationships between predictor variables and the outcome variable of interest, ovarian failure recovery. A multivariate logistic regression model was determined by the variable selection technique stepwise regression, which provided the optimal fitting model predictive of ovarian failure recovery. All statistical analyses were performed on version 4.0.4 of RStudio (The R Project for Statistical Computing).

Results

Study population

Thirty-six patients with at least two instances of FSH elevation and a history of childhood cancer between August 2011 and August 2021 were identified. The characteristics of this group are summarized in Table 1.

Table 1: Demographics.

	Overall (n=36)
Recovery	
No	26 (72.2 %)
Yes	10 (27.8 %)
Diagnosis_overall	
Other	17 (47.2 %)
ALL	13 (36.1 %)
AML	6 (16.7 %)
Specific diagnosis	
ALL	13 (36.1 %)
AML	6 (16.7 %)
Brain	8 (22.2 %)
Other	6 (16.7 %)
Solid tumor	3 (8.3 %)
Cancer treatment	
Combination	24 (66.7 %)
Alkylating agent	11 (30.6 %)
Other	1 (2.8 %)
Radiation	
No	10 (27.8 %)
Yes	26 (72.2 %)

Table 1: (continued)

	Overall (n=36)
Type of radiation	
Other	8 (22.2 %)
Pelvic	3 (8.3 %)
TBI	14 (38.9 %)
Hormone therapy	
No	10 (27.8 %)
Yes	26 (72.2 %)
Type of hormone therapy	
Combination	10 (27.8 %)
Oral	3 (8.3 %)
Transdermal	13 (36.1 %)
GnRHa	
No	30 (83.3 %)
Yes	6 (16.7 %)
Age at diagnosis	
Median (IQR)	8.00 (7.25)
Age at FSH increase	
Median (IQR)	12.5 (5.00)
Age	
Median (IQR)	16.0 (6.25)
FSH peak	
Median (IQR)	77.9 (36.7)
Fertility planning	
No	23 (63.9 %)
Yes	13 (36.1 %)
Peak AMH	
Median (IQR)	0.0300 (0.140)

Table 2: Factors associated with recovery.

	No (n=26)	Yes (n=10)	p-Value
Age at diagnosis			
Median (IQR)	9.00 (6.00)	6.00 (7.00)	0.2875
Age at FSH increase			
Median (IQR)	12.5 (4.75)	12.5 (3.50)	0.7225
Diagnosis_overall			
Other	10 (38.5 %)	7 (70.0 %)	0.1669
ALL	10 (38.5 %)	3 (30.0 %)	
AML	6 (23.1 %)	0 (0 %)	
Specific diagnosis			
ALL	10 (38.5 %)	3 (30.0 %)	0.0807
AML	6 (23.1 %)	0 (0 %)	
Brain	3 (11.5 %)	5 (50.0 %)	
Other	4 (15.4 %)	2 (20.0 %)	
Solid tumor	3 (11.5 %)	0 (0 %)	
Cancer treatment			
Combination	21 (80.8 %)	3 (30.0 %)	0.0069
Alkylating agent	5 (19.2 %)	6 (60.0 %)	
Other	0 (0 %)	1 (10.0 %)	
Radiation			
No	9 (34.6 %)	1 (10.0 %)	0.2227
Yes	17 (65.4 %)	9 (90.0 %)	
Type of radiation			
Other	3 (11.5 %)	5 (50.0 %)	0.1015
Pelvic	3 (11.5 %)	0 (0 %)	
TBI	11 (42.3 %)	3 (30.0 %)	
Hormone therapy			
No	4 (15.4 %)	6 (60.0 %)	0.0136
Yes	22 (84.6 %)	4 (40.0 %)	
Type of hormone therapy			
Combination	8 (30.8 %)	2 (20.0 %)	1
Oral	3 (11.5 %)	0 (0 %)	
Transdermal	11 (42.3 %)	2 (20.0 %)	
GnRHa			
No	21 (80.8 %)	9 (90.0 %)	0.6546
Yes	5 (19.2 %)	1 (10.0 %)	

The most common type of cancer identified in this group of patients was ALL, accounting for 13 (36.1 %) cases. Six (16.7 %) patients had a diagnosis of AML, 8 (22.2 %) had diagnoses of brain cancers, 3 (8.3 %) had solid tumors, and the remaining 6 (16.7 %) had other malignancies (Table 2). Types of cancers identified in the "other" category included Hodgkin lymphoma, chronic myelogenous leukemia (CML), T-cell lymphoma, hemophagocytic lymphohistocytosis, and T-myeloid acute leukemia. The mean age of cancer diagnosis was 8.5±4.3 years.

Nearly all patients (97.2 %) were treated with alkylating agents, such as cyclophosphamide, as a part of their chemotherapy regimen, and 66.7 % of total patients received alkylating agents in combination with either bone marrow or stem cell transplant. The majority of patients (72.2 %) also received some form of radiation therapy, with 14 (38.9 %) patients receiving total body irradiation and 3 (8.3 %) receiving radiation directly to the pelvis (Table 2).

The mean peak in FSH was 75.2±34.5 mIU/mL, and the mean age at FSH increase (at the time of the peak FSH value) was 12.6±2.8 years. Twenty-five patients (69.4 %) had AMH levels checked during the 10-year study duration, but the value was <1 ng/mL in all subjects. Most patients (72.2 %) received some form of hormone therapy including transdermal estrogen, oral estrogen, and/or an oral contraceptive pill (OCP). Transdermal hormone therapy alone (36.1 %) and combination oral-transdermal therapies (27.8 %) were more common than oral hormone therapy alone (8.3 %). Fertility planning was offered or discussed in 36.1 % of patients (Table 2). Patients not receiving hormone therapy were those who had recovered ovarian function, excepting one patient who began treatment after the study period.

Factors associated with POI recovery

Ten patients (27.8 %) were noted to have some degree of recovery in their ovarian function (normalization of FSH values to Tanner stage and age adjusted lab reference values). Among these individuals, 60.0 % received alkylating agents as a part of their chemotherapy regimen and 30.0 % received alkylating agents in combination with transplant, while all individuals without recovery of ovarian function received these agents either alone or with transplant (p=0.0069). Treatment with alkylating agents alone (without transplant) was associated with improved odds of recovery in univariate modeling (OR: 8, 95 % CI: 2–52, p=0.01) (Table 3). Additionally, only 40.0 % of patients demonstrating recovery received hormone therapy, as compared to 84.6 % of patients without recovery (p=0.0136). Accordingly, receiving hormone therapy was associated with a reduced odds of recovery in univariate analyses (OR: 0.1, 95 % CI: 0.02–0.6, p=0.01) (Table 3). Multivariate regression modeling revealed that age at diagnosis and type of cancer treatment were significant predictors of POI recovery. Specifically, each year older in age was associated with a 30 % decrease in odds of recovery (OR: 0.7, CI: 0.5–0.95, p=0.035), and treatment with an alkylating agent without transplant was associated with a 3-fold increase in odds of recovery (OR: 3, CI: 2.7–564, p=0.007) (Figure 1, Table 4).

Table 3: Univariate modeling.

Variable	p-Value	Odds ratio	2.5 %	97.5 %
Age at diagnosis	0.34	0.9	0.8	1.1
Age at FSH increase	0.73	1	0.7	1.2
Diagnosis (overall)	0.30	0.4	0.07	2
Diagnosis (AML)	0.99	1e-08	*NA*	1e+101
Cancer treatment (alkylating agent)	0.01	8	2	52
Cancer treatment (other)	0.99	1e+08	8e-205	*NA*
Radiation (yes)	0.17	5	0.7	95
Hormone therapy (yes)	0.01	0.1	0.02	0.6
GnRHa (yes)	0.51	0.5	0.02	3.5

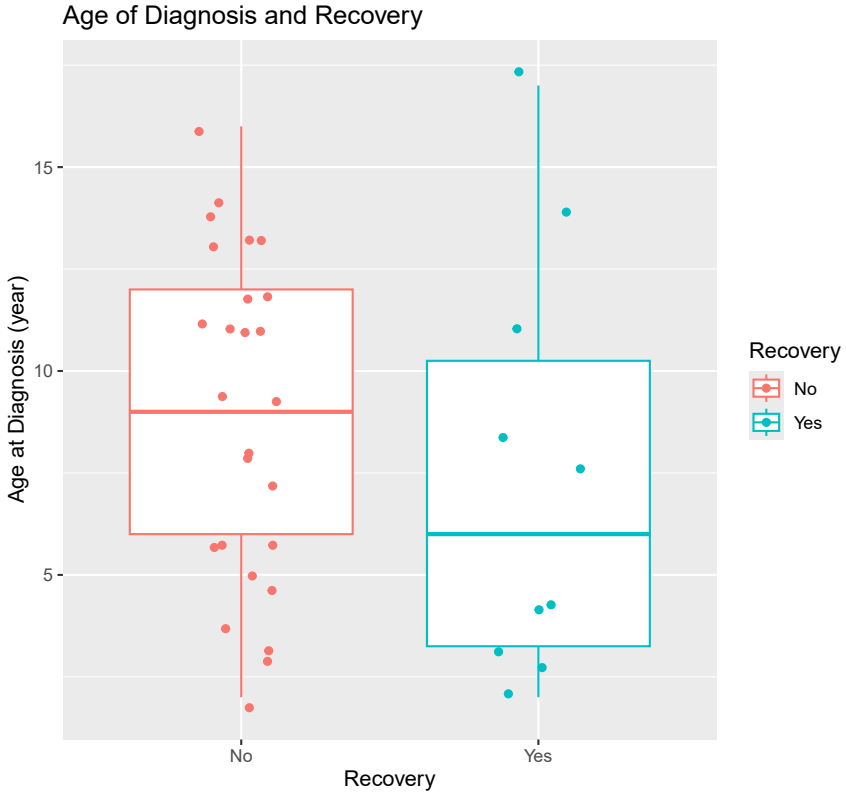

Figure 1: Boxplot of age breakdown.

Table 4: Multivariate modeling.

Variable	p-Value	Odds ratio	2.5 %	97.5 %
Age at diagnosis	0.035	0.7	0.5	0.95
Age at FSH increase	0.086	2	0.97	2.7
Cancer treatment (alkylating agent)	0.007	3	2.7	564
Cancer treatment (other)	0.993	6e+08	2e-203	*NA*

Discussion

Though rare, premature ovarian insufficiency can occur in pediatric cancer survivors and more information is needed for this unique patient population and their prognosis. To address this knowledge gap, we conducted a 10-year retrospective review of 36 patients with POI at a major children's hospital and uncovered the following important clinical insights [1]: common features of this population included diagnoses of ALL (13, 36.1 %) and AML (6, 16.7 %), radiation therapy (26, 72.2 %), combination treatment (24, 66.7 %, defined as bone marrow transplant and any alkylating agent), and hormone therapy (26, 72.2 %) [2]; the majority of patients did not have documented fertility planning (23, 63.9 %); and [3] younger age of cancer diagnosis significantly predicted improved odds of ovarian function recovery, with a one unit increase in age at diagnosis associated with a 29 % decrease in odds of recovery. This finding that patients diagnosed with primary ovarian insufficiency, especially if they were diagnosed with cancer at a younger age, may potentially recover ovarian function should be considered when counseling patients about their treatment options and prognosis. Given the psychosocial complexity in disclosing odds of ovarian function recovery to patient and their families, regardless of one's pubertal status or cancer status, care and sensitivity should be taken to present this statistic objectively during counseling and recognize the individuality of each patients' recovery trajectory. Future studies with larger sample sizes are needed to sub-stratify cohorts based on pubertal status and verify this finding.

Our study revealed that younger age of cancer diagnosis is associated with increased likelihood of ovarian function recovery. This finding is consistent with a report by Thomas-Teinturier et al., who conducted a cohort study of childhood cancer survivors with POI and found that women treated with alkylating agents after puberty onset (and thus of older age), had the highest risk ratio for non-surgical menopause of all groups evaluated [3]. Our retrospective review thus emphasizes the importance of routine surveillance for ovarian failure in pediatric patients diagnosed with cancer at an early age, especially abnormal uterine bleeding due to anovulatory cycles with some retainment of follicular function, a common presenting symptom of early stage POI [10]. While the etiology of primary ovarian insufficiency in the pediatric population remains largely unknown, a single-center review by Brauner et al. reported multiple possibilities [11]. Here, the authors reviewed 17 normal 46, XX karyotype girls with primary ovarian insufficiency and determined etiology in 8 cases, including cerebellar ataxia secondary to congenital disorder of glycosylation type 1 (3 cases), mitochondrial disease (2 cases), autoimmune deficiency/AIRE mutation (1 case), and NR5A1 mutation (2 cases). Consistent with their findings, Michala et al. also suggested that genetic mutations, most commonly *FMR1* premutation, represent an important risk factor for premature ovarian insufficiency in adolescence and thus early genetic counseling may improve the odds of earlier diagnosis [10]. While it was beyond the scope of our paper to affirm the specific etiology behind POI in this study sample of cancer patients, we encourage monitoring for POI in pediatric cancer patients as they may represent an entirely different etiology to improve the likelihood of early diagnosis (especially if combined with any of the aforementioned risk factors, potential etiologies, or symptoms) and, thus, of subsequent recovery. Future studies evaluating outcomes such as bone density and quality of life measures in these patients will be helpful to determine how these patients should continue to be monitored and treated to obtain the best possible outcomes.

One surprising finding was that only a small proportion of patients had documented fertility planning. Infertility is a potential side effect of certain cancer treatments, with childhood cancer survivors having a 38 % reduction in the likelihood of pregnancy compared to the general population [12]. Specifically, radiation to the uterus (dose >5 Gy; relative risk 2.48; 95 % CI, 1.54–4.01) [13] and survivors of CNS tumors [14] are both associated with an increased risk of infertility. Extending this finding to our population, nearly one in four patients were diagnosed with CNS tumors and over 70 % of patients received radiation, yet the majority of patients did not receive fertility planning. Given the high risk of infertility associated with certain cancer treatments, this observation calls for improved fertility planning in these patients. AMH, which is an indirect marker of ovarian reserve, is not used to diagnose POI but can be used in addition to FSH and estradiol when assessing the potential for future fertility [15]. However, given the single-center nature of our study, future multi-institutional analyses and larger, population-based surveillance are needed to further characterize trends in fertility planning and conservation measures for pediatric cancer patients,

especially before development of POI. Discussions regarding the impact of treatment on fertility and potential methods of fertility preservation are important to have with these patients and their families to set expectations and improve quality of life.

Limitations

This study is subject to several limitations. First, the small sample size limits the statistical power and, thus, the conclusive findings that can be drawn from the data. However, premature ovarian insufficiency in pediatric cancer patients is rare and our 10–year experience consisting of 36 patients proves significantly larger than previous studies of similar scope [11, 16, 17]. Second, this study included data reviewed from a pediatric institution that serves a large population in Southern California. However, this single center design may nonetheless limit the generalizability of these findings and future multi-center studies from diverse patient populations are needed to validate the present findings. Third, while this study did evaluate type of chemotherapy received, it was not powered to evaluate associations with individual drugs, nor did it address the dose used. The apparent statistical significance of chemotherapy type suggesting that those receiving combination therapy (alkylating agent and bone marrow/stem cell transplant) recovered less often than those receiving alkylating agents alone may possibly be attributed to a higher severity of disease requiring more aggressive treatment in the former group and limited by the near totality of patients having a history of alkylating agent exposure. Additionally, evaluation and application of potential late effects of chemotherapy is inherently limited by the rapidly evolving nature of the field.

Conclusions

This retrospective review demonstrates that, while uncommon, POI can occur in pediatric cancer survivors, emphasizing the importance of educating patients on the potential long-term effects of cancer treatment and routine surveillance for these complications. This study also confirmed that recovery of ovarian function is possible in these patients, especially when diagnosed at a younger age, so continued monitoring is necessary. Prospective studies and randomized clinical trials evaluating the contributory factors for POI development, treatment, and recovery will be necessary to determine how these patients can be best treated.

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