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ORIGINAL ARTICLE

Ovarian reserve and premature ovarian failure in girls and adolescents after hematopoietic stem cell transplantation

Reserva ovárica y falla ovárica prematura en niñas y adolescentes postrasplante de progenitores hematopoyéticos

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What do we know about the subject matter of this study?

Diminished ovarian reserve and premature ovarian failure in childhood cancer survivors are among the late effects that most impact the quality of life in adulthood.

What does this study contribute to what is already known?

This study shows the reality in a Latin American country. 100% and 72% of the patients presented a decrease in the reserve and premature ovarian failure post-HSCT, respectively, giving priority to early intervention for hormone replacement therapy.

Abstract

The increased survival of children and adolescents after Stem Cell Transplantation (SCT) has allowed us to gain a better understanding of the late effects that this procedure might have. **Objective:** to measure ovarian function and reserve after SCT. **Patients and Method:** A descriptive, observational, and cross-sectional study of girls and adolescents with SCT between 1999 and 2011. External gynecologic examination, hormone tests, and abdominal gynecologic ultrasound were performed, observing pubertal development pre-SCT. The following data from the clinical record were recorded: baseline pathology, type of conditioning, use of radiotherapy in conditioning, age at the time of SCT,

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and history of acute or chronic graft-versus-host disease (GVHD). Hormonal tests included follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin (PRL), thyroid-stimulating hormone (TSH), free thyroxine, total testosterone, sex hormone-binding globulin (SHBG), and anti-Müllerian hormone (AMH). Statistical analysis included the chi-square or Fisher's Exact test with a p-value < 0.05. **Results:** 41 patients were evaluated. The median age at the time of SCT was 6.8 years (1.5-14.1) and the median age at evaluation was 14.8 years (range: 4-25.4 years). 93% of the transplants were in patients with oncological disease and with myeloablative conditioning regimens. All patients presented decreased ovarian reserve, and 72% showed Premature Ovarian Failure (POF). **Conclusions:** All patients had decreased ovarian reserve and most of them had a high prevalence of POF. Before SCT, a gynecological evaluation and subsequent follow-up for hormone monitoring and initiation of hormone replacement are essential.

Introduction

In 1999, the pediatric hematopoietic stem cell transplantation (HSCT) program was initiated in the Chilean public health system, which has performed most of the HSCTs in patients with cancer, reporting an overall survival rate of 62% at 5 years[1,2]. The systematic increase in the survival of transplanted patients, with or without cancer, has exposed us to the late effects of this therapy[3,4].

Pre-HSCT treatment and conditioning for HSCT often require the administration of high doses of chemotherapy and/or radiotherapy. These therapies are associated with diminished ovarian reserve (DOR) and premature ovarian failure (POF) and, therefore, endocrine disruption and infertility in up to 85% of patients[2,4-7]. Ovarian reserve depends on the quantity and quality of the antral follicles, which predictably decreases physiologically during life[7,8]. Anti-Müllerian hormone (AMH) is a marker of the ovarian reserve since its levels correlate with the primordial follicles endowment[9].

The POF post-HSCT triggers infertility and menopause[10], and its early diagnosis would allow timely treatment with hormone replacement. No evaluation of ovarian reserve and POF post-HSCT has been reported so far in the Latin American scientific literature. The objective of this study was to evaluate the ovarian reserve and the prevalence of POF in post-HSCT girls and adolescents in a cohort of a public pediatric hospital of national reference for HSCT.

Patients and Method

Descriptive, observational, cross-sectional study conducted between February 2013 and January 2015. All female patients who received HSCT at the *Hospital Luis Calvo Mackenna* between 1999 and 2011 were invited to participate. The study was approved by the corresponding pediatric scientific ethics committee.

Population and sample

All patients alive and under follow-up at the time of evaluation, in remission of their baseline pathology, and with only one HSCT performed were included. Inclusion criteria were to have at least one ovary and not to have received corticosteroid treatment in the last 3 months.

Even though the sampling method was not random, the sample size was calculated for the estimation of the proportion of DOR or POF post-HSCT. It was observed that 43 patients were enough for a 95% Confidence Interval (95%CI), with 5 percentage units of accuracy for the hypothesis of a population frequency of around 80%, in line with what has been described in the literature[11]. This calculation included a replacement rate of 10% to prevent loss of subjects due to any cause.

Procedures

Initially, the clinical records were reviewed, and the patients who agreed to participate were asked to attend the study and signed the informed consent for the evaluation to be physically examined and perform an external or internal gynecological examination in patients who started to be sexually active They were scheduled for a hormonal study sample collection and an abdominal gynecologic ultrasound.

The following data were recorded from the clinical record: baseline pathology, type of conditioning, use of radiotherapy in conditioning, age at the time of HSCT, and having had or had acute or chronic graft-versus-host disease (GVHD).

In the clinical evaluation, age at study entry, nutritional status by body mass index, pubertal development according to Tanner scale[12], age at the onset of menarche, menstrual cycles, pregnancies, abortions, and use of hormone replacement therapy or contraception were determined.

The levels of the following hormones were measured: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin (PRL), thyroid-sti-

mulating hormone (TSH), free thyroxine (FT4), total testosterone, sex hormone-binding globulin (SHBG), and anti-Müllerian hormone (AMH).

In patients with regular menstrual periods, the sample was collected between days 3 and 5 of the cycle, considering the first day of menstruation as day one of the cycle. If the patient presented amenorrhea or pre-menarche, the sample was collected at any time. If she was using oral contraception, it was discontinued for 30 days before collecting the sample. If she was receiving hormone replacement therapy, treatment was suspended for 5 to 7 days before collecting the sample. Fasting was 8 hours, and the sample was collected before 9 AM.

The samples were processed in 2 laboratories; the hospital's laboratory processed TSH and FT4, and an external and accredited laboratory processed FSH, LH, estradiol, PRL, total testosterone, SHBG, and AMH, using the enzyme immunoassay method (ELISA), with 0.1 ng/ml of sensitivity, KIT (Beckman coulter Inc., Brea, CA, USA).

The ultrasounds were performed by three professionals with pediatric experience, according to the following pre-established protocol: a Phillips (ATL) 5000 ultrasound machine with convex (5HZ) and linear (12HZ) transducer was used, using the suprapubic space in both prepubertal and post-pubertal patients. The uterus was measured along its longitudinal and transverse axis (cm), and then the anteroposterior axis (cm) was measured at the level of the uterine corpus and cervix, where the index between measurements was calculated. In addition, the endometrial line (mm) was measured.

The pubertal uterus was defined as pyriform in shape where the corpus is larger than the cervix, with a 3:1 ratio. The prepubertal uterus was defined as having a tubular morphology with a 1:1 ratio. Also, the longitudinal (L), transverse (T), and anteroposterior (AP) axes were measured in cm in the ovaries. The volume (V) was calculated with the formula:

The total number of antral follicles was determined by counting from the upper pole of the ovary to the lower pole. In addition, the length of the major axis (mm) was measured and classified as greater or less than 10 mm.

In post-menarchic patients with regular menstrual cycles, the ultrasound study was performed in the early follicular phase, between days 1 to 5 of the cycle. In pre-menarchic patients, with amenorrhea or under hormone replacement therapy, it was performed at the time of clinical evaluation[13].

Definitions of variables

POF was defined as patients with menarche, presenting amenorrhea of 4 months or more, before the age of 40 years (at the time of evaluation for the participants of this study) with FSH higher than 25 mIU/L and estradiol less than 20 pg/ml[14]. This group also includes patients with primary ovarian failure who presented absence of spontaneous pubertal development at 13 years of age with primary amenorrhea associated with FSH higher than 25 mIU/L.

Primary amenorrhea was defined as the absence of menarche after the age of 13 years without development of secondary sexual characteristics, or after the age of 15 years with development of secondary sexual characteristics. Patients without menarche 3 to 5 years after their thelarche were also considered within this definition[15]. Secondary amenorrhea was defined as the absence of menstrual cycles in 3 months[15,16].

DOR was defined considering AMH as the priority parameter, which for post-pubertal patients should be less than 0.7 ng/ml. Secondarily, the antral follicle count was evaluated, which should be < 6 and with a diameter < 10 mm in 2 dimensions, with an ovarian volume < 3 ml or a diameter < 2 cm. However, in prepubertal patients there are no standardized definitions of ovarian reserve[17], so the values of the Almog's age-related nomogram[18] of the AMH levels were used as a reference, establishing the 3rd percentile as 0.38 ng/ml in those under 24 years of age.

Study groups

The sample was divided into 2 groups for data analysis. The first group (G1) consisted of patients without Tanner pubertal development and younger than 13 years. The second group (G2) consisted of patients with pubertal development by Tanner independent of age or without pubertal development by Tanner, but older than 13 years.

Statistical analysis

First, the data of each group were analyzed with summary or frequency statistics in order to establish the characteristics of the patients studied regarding age, baseline pathology, type of conditioning, pubertal development, nutritional status, pregnancies and abortions, results of the hormonal study, abdominal gynecological ultrasound, and physical and gynecological examination. The 95%CI was then estimated for the ratio of DOR and POF post-HSCT.

Finally, for G2, the association between POF and conditioning (myeloablative and non-myeloablative), use of busulfan or radiotherapy, and acute and chronic GVHD were analyzed. These analyses were performed with the chi-square test and alternatively, Fisher's Exact was used for cases in which the number of subjects within any cell of the table was less than 5. The significance level was established as $p < 0.05$ and the statistical package used was STATA version 16.

Results

At the time of the study, 258 HSCT had been performed in 249 patients at the HLCM, where 91 of them were female. Of these patients, 32 had died at the time of evaluation; 59 of them were alive, 6 had dropped out of the follow-up, 8 did not meet other inclusion criteria, and 4 did not agree to enter the study. Finally, 41 patients were evaluable, accounting for about 80% of the population (Figure 1).

Table 1 summarizes the history of HSCT and clinical characteristics at study entry according to groups. Table 2 describes the characteristics of the pubertal development of the patients. In relation to the baseline pathology, 38 patients had oncologic diagnoses, where the most frequent were acute lymphoblastic leukemia and acute myeloblastic leukemia. Only 3 patients had non-oncologic underlying pathologies (one Kostmann neutropenia and 2 severe aplastic anemia). Regarding the type of HSCT, 6 patients received autologous and 35 allogeneic transplants. GVHD only occurred in allogeneic transplants (Table 1). Seventeen patients received total body radiotherapy of 12 Gy in 6 fractions.

At the time of the study, two patients had had children, one before the study and one during the study; one of them was premature and, at the time of closing the study both were healthy. No patient reported spontaneous or induced abortions.

Forty patients were evaluated with an ultrasound study since one did not show up. Tables 3 and 4 summarize the results of the hormonal and ultrasound study of both groups. In Group 1, estrogen levels were very low for the age. In Group 2, 100% of the patients met DOR criteria, in addition, 72% of them (95%CI: 54% to 88%) had signs of POF and, of the same 72%, 36% (95%CI: 18% to 53%) had primary ovarian failure. Only 58% of the patients were receiving hormone replacement therapy. Since transabdominal ultrasound was used in 10 patients, it was not possible to visualize the ovaries in any of them.

Sixteen patients were younger than 13 years at the time of the evaluation, three of them had normal puberty. In Group 2 of age older than 13 years, mean FSH and estradiol levels were 61.9 mIU/ml and 14.8 pg/ml, respectively, and were within the range of POF.

In this study, we found a statistical association between POF and RDT ($p = 0.041$), however, it could not be established which type of RDT was the most significant in affecting ovarian function possibly due to the insufficient sample size. No other significant differences were found in other variables studied such as myeloablative conditioning or reduced intensity, or busulfan administration. We also found no significant differences with pubertal development at the time of HSCT or after HSCT, development of acute GVHD, chronic GVHD, and risk of amenorrhea.

Discussion

This is a multidisciplinary study on DOR and POF in girls, adolescents, and young women post-HSCT. It is the first publication in Latin American patients. Most of them were younger than 20 years (93%) and this casuistry would surpass in number previously published studies[6,19,20]. In addition, the patients were evaluated from a gynecologic, hormonal, and imaging approach, which has not been the case in previous studies[16,21].

In this study, 100% of the post-pubertal adolescents had DOR and a prevalence of POF of up to 72%. This finding is lower than that described in the literature, which reaches values of up to 80%[11] since the median age of the population studied was only 14 years, and this correlates with menstrual disorders that reach up to 86% between amenorrhea and oligomenorrhea.

If we compare patients with the general population of women under 20 years of age, POF affects only 0.01%[22], which is 6000 times less than that found in our study. Even in the general population of women over 40 years of age, POF affects only 1%[23]. The incidence of post-HSCT POF in adults ranges from 54% to 86%[6].

In girls under 13 years of age without pubertal development, we found extremely low estrogen levels, a finding that, in the literature, has been correlated with

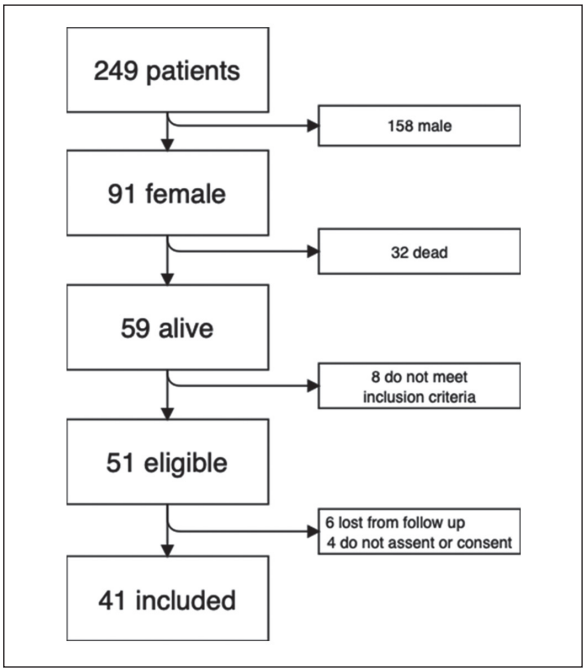

Figure 1. Patients included.

Table 1. Patients characteristics at time of the evaluation of the study

Parameters	Group 1 N = 13	Group 2 N = 28
Age (years). Median and range		
At transplant	3.3 (1-6)	6.8 (2-14)
At time of the evaluation	6.2 (4-10)	15.9 (13-25)
Oncological Pathology	13 (100%)	25 (89%)
Conditioning		
Myeloablative	11	27
Reduced Intensity	2	1
Radiotherapy	5	20
Type of Transplant		
Autologous	4	2
Allogeneic	9	26
Acute GvHD, n (%)		
No	0 (0%)	4 (15%)
Grades (2-4)	5 (55%)	12 (46%)
Grades (3-4)	1 (11%)	2 (8%)
Chronic GvHD, n (%)		
No	7 (78%)	16 (61%)
Limited	0 (0%)	2 (8%)
Extensive	2 (22%)	8 (31%)
Nutritional Status		
Eutrophic	4	17
Obesity	5	2
Overweight	3	6
Malnutrition	1	3
Pregnancy	0	2

Abbreviations: GvHD: Graft versus Host disease. Group 1: without pubertal development and under 13 years of age. Group 2: with pubertal development and 13 years or older.

Table 2. Pubertal development and menstrual cycles at time of SCT and during evaluation after SCT

Parameter	SCT N = 41	Evaluation N = 41
Age mean ± SD	6.8 ± 3.7	14.8 ± 5.5
Pubertal development		
Pre-pubertal	35	13
Pubertal	6	28
Menstrual cycles		
Primary Amenorrhea	0	14
Secondary Amenorrhea	3[(a)]	2
Oligomenorrhea	1	8
Normal	2	4
No apply[(b)]	35	13

[(a)]Amenorrea secundaria: por supresión hormonal. [(b)]No le corresponde por edad o inicio puberal sin menarquia antes de los 13 años. Abreviaciones: TPH: Trasplante de Progenitores Hematopoyéticos, DE: desviación estándar.

Table 3. Hormonal study during follow-up after stem cells transplantation

Parameters	Group 1 N = 13	Group 2 N = 28
AMH (ng/ml)		
Median ± SD	0.1 ± 0.003	0.1 ± 0.052
Range	0.1-0.11	0.1-0.3
FSH (mUI/ml)		
Median ± SD	6.8 ± 19	44.5 ± 48
Range	1.0-69.0	10.0-186.0
LH (mUI/ml)		
Median ± SD	0.24 ± 3.11	10.35 ± 25.28
Range	0.1-11.6	0.6-115.0
Estradiol (pg/ml)		
Median ± SD	< 5.0 ± 2.88	12.0 ± 11.36
Range	< 5.0-12.0	< 5.0-62.0
Prolactina (ng/ml)		
Median ± SD	10.2 ± 7.93	9.4 ± 21.62
Range	5.4-35.0	2.0-96.0
Testosterona		
Median ± SD	0.07 ± 0.065	0.33 ± 0.13
Range	0.05-0.25	0.2-0.62
SHBG		
Median ±SD	85 ± 29	32.45 ± 29.37
Range	42-151	12-116

Abbreviations: AMH: Antimüllerian Hormone, FSH: Follicular Stimulant Hormone, LH: Luteinizing Hormone, SD: standard deviation, SHBG: Sex Hormone Binding Globulin. Group 1: without pubertal development and under 13 years of age. Group 2: with pubertal development and 13 years or older.

Table 4. Gynecological ultrasound results

Parameters	Group 1 N = 13	Group 2 N = 27
Characteristics of Uterus (N)		
Pre-pubertal	12	11
Pubertal	1	16
Ovarian (means and range)		
Volume	0.24 (0.1-1.0)	1.4 (0.2-5.3)
Longitudinal diameter	1.1 (0.4-1.8)	1.7 (1.0-4.7)
Antral Follicles < 10 mm (mean and range)		
Right ovary	1 (0-4)	1,35 (0-6)
Left ovary	1 (0-5)	1 (0-3)

Group 1: without pubertal development and under 13 years of age. Group 2: with pubertal development and 13 years or older.

alterations in cognitive and behavioral development, and in the process of bone mineralization, which poses a question as to whether it is appropriate to substitute estrogens early in them[2-246]. On the other hand, there is no consensus on the definition of DOR in the pediatric age. For this reason, only the results are described and, based on the historical values of AMH, all these girls would have a DOR according to the definition in adulthood[18].

AMH has emerged as a good marker of ovarian reserve[16,27] because it reflects the number of growing preantral follicles, independent of gonadotropin values and the use of hormone replacement therapy[28]. At the same time, in some post-HSCT patients, a transient reduction in AMH levels has been observed during the first year, with spontaneous recovery[19], which was not observed in our study. In contrast to this study and in agreement with that published by Wedrychowicz, we observed a decrease in AMH levels in 100% of the patients[20]. These findings could be because 96% of the patients received myeloablative conditioning regimens with radiotherapy in 71% of them, which has been described in the literature, and the current recommendation, as far as possible, is to use less aggressive conditioning regimens to affect the ovarian reserve to a lesser extent, as long as the same cure rate is achieved for the patients[11].

The high prevalence of DOR and POF implies a high risk of developing early menopause and infertility. Early menopause is a chronic and incurable condition that requires timely hormone replacement, according to her stage of pubertal development[23]. This therapy aims to prevent osteoporosis, dyspareunia, premature aging, learning disorders, and other symptoms associated with hypoestrogenism in order to improve self-esteem and quality of life[30,313]. Early referral to pediatric gynecology and endocrinology with expertise in pubertal development is recommended[29].

Regarding fertility, despite the high prevalence of DOR and POF, two patients had a spontaneous pregnancy, with two live and healthy newborns. This demonstrates that it is possible for post-HSCT patients to become pregnant and thus, on the part of the treating team, to establish a dual approach that, on the one hand, educates patients and their families about contraceptive treatment and, on the other hand, provides psychological support due to the high risk of infertility, in order to advise on fertility preservation in relation to ovarian tissue cryopreservation, egg donation, embryo donation, and adoption[3-315].

Our study has the following limitations: 1. The international recommendation is to evaluate through transvaginal ultrasound, but it is impossible to practice in most pediatric patients, so it is generally performed through transabdominal ultrasound[14,17,36]; 2. The definition of POF was published after the design of this study, and we only have one FSH measurement; and 3. The lack of a contemporary control group.

Despite this, we believe that our findings raise new needs and challenges such as carrying out long-term follow-up and evaluating the needs of survivors regarding fertility, maternity, and contraception, as well as their adherence to hormonal treatment that should last at least until the age of 50, developing a national program for fertility preservation in girls and adolescents with cancer[14,35,36]. Finally, it is necessary to create strategies to achieve an adequate transition from pediatric to adult care in our country.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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