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# Ovarian Function and Spontaneous Pregnancy After Hematopoietic Stem Cell Transplantation for Leukemia Before Puberty: An L.E.A. Cohort Study

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## HIGHLIGHTS

- Spontaneous puberty is possible after hematopoietic stem cell transplantation
- Spontaneous pregnancies are possible after hematopoietic stem cell transplantation
- Older age at transplantation is a risk factor for premature ovarian insufficiency
- Contraceptive methods is needed even if there was an induction of puberty

**TITLE PAGE**

*Article title* : Ovarian function and spontaneous pregnancy after hematopoietic stem cell transplantation for leukemia before puberty

An L.E.A. cohort study

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**ABSTRACT**

**Background:** Ovarian function impairment and infertility are among the most frequent late effects after hematopoietic stem cell transplantation (HSCT).

**Objective:** The aim of this study was to evaluate ovarian function, occurrence of premature ovarian insufficiency (POI), and spontaneous pregnancy in a large cohort of adult survivor women who had received HSCT for leukemia before puberty.

**Study design:** We conducted a retrospective observational study in women from the national cohort L.E.A., the long term French follow-up program after childhood leukemia.

**Results:** The median follow-up duration was 18 years [14.2-23.3] after HSCT. Among 178 women, 106 (60%) needed pubertal induction with hormone substitution treatment, whereas 72 (40%) had spontaneous menarche. After spontaneous menarche, 33 (46%) developed POI, mostly within 5 years of HSCT. Older age at time of HSCT and cryopreservation of ovarian tissue appeared as significant risk factors for POI. More than 65% of patients who underwent HSCT before the age of 4.8 years had spontaneous menarche and almost 50% didn't have POI at last evaluation whereas more than 85% with HSCT after the age of 10.9 years didn't have spontaneous menarche and needed induction of puberty with hormone replacement therapy. Twenty-two women (12%) had at least one spontaneous pregnancy, with 17 live-births, 14 miscarriages, 4 legal abortions and 2 therapeutic abortions.

**Conclusion:** These results add supplementary data to better counsel patients and their families on the chances of ovarian residual function and pregnancy post-HSCT as well as on the potential interest of fertility preservation.

**KEYWORDS**

Leukemia, Premature ovarian insufficiency, Hematopoietic stem cell transplantation

## INTRODUCTION

Leukemia is the most common childhood cancer, accounting for one third of cases. Over the last decades, innovation in diagnosis and treatment have increased the overall survival rate to over 80 %.<sup>1</sup> The remarkable improvement in the prognosis of children with acute leukemia (AL) has been mainly achieved through the administration of risk-adapted therapy, including intensive chemotherapy and hematopoietic stem cell transplantation (HSCT). As a consequence, there is a growing population of adult survivors that will face the long term side effects of cancer treatments such as growth failure, hypothyroidism, gonadal or uterine dysfunction or alteration of quality of life.<sup>2,3</sup> Indeed, Berbis and al in 2013 described that more than 70% of childhood leukemia survivors from the French cohort L.E.A. (Leucémie de l'Enfant et de l'Adolescent) were found to have at least one late side effect.

The human ovary contains a fixed number of non-growing follicles (NGFs) established before birth that declines with age until the menopause occurs, physiologically around the age of 50. Ovarian reserve damage causes hypergonadotropic hypogonadism with a high risk of premature ovarian insufficiency (POI), defined by ESHRE (European Society of Human Reproduction and Embryology) as oligo/amenorrhea for at least 4 months, and an elevated FSH level  $> 25$  IU/l on two occasions  $> 4$  weeks apart before the age of 40.<sup>4</sup> The ovarian reserve is particularly sensitive to the toxicity of cancer treatment, especially conditioning regimens preparing for HSCT, which cause disorders of both endocrine and reproductive functions. Indeed, POI and infertility are among the most frequent late effects after HSCT.<sup>2,5</sup> POI includes pubertal development impairment; amenorrhea can be primary but also secondary depending on the residual post-HSCT ovarian reserve. According to various published data, the incidence of POI ranges from 44 to 100% patients who received HSCT in childhood for either malignant or non-malignant hematological disorders.<sup>6-8</sup> Risk factors for POI after HSCT have been described : younger age at HSCT predicted spontaneous

menarche whereas myeloablative conditioning (MAC) regimen was shown as the main risk factor for ovarian failure.<sup>9</sup> Indeed, the age at HSCT is known to be critical for ovarian function : HSCT in prepubertal girls means better chances of recovery and achievement of puberty.<sup>5,10,11</sup>

Fertility impairment in women transplanted during childhood and adolescence is high, ranging around 83%.<sup>5</sup> Pregnancy rate after HSCT is described in the literature as quite low, below 1%.<sup>12,13</sup> In this context, fertility preservation before HSCT remains a major challenge for childhood cancer survivors.

In AL, ovarian stimulation and oocyte vitrification is possible only after puberty, often constrained by cancer treatment emergency and not recommended immediately after the first-line of chemotherapy cycles due to a mutagenic risk. In AL and for prepubertal girls, the only fertility preservation strategy available before HSCT is ovarian tissue cryopreservation (OTC).

The aim of our study was to evaluate puberty development, long term ovarian function, and occurrence of spontaneous pregnancy on a population of prepubertal HSCT survivors who underwent HSCT for acute leukemia in childhood.

## MATERIALS AND METHODS

### *Characteristics of childhood cancer survivor women*

Women described here were all included in the L.E.A. program. L.E.A. is the long-term follow-up program involving childhood acute leukemia survivors in France. Patients were included in L.E.A. if they met the following criteria: treated for acute leukemia after 1980 in one of the participating centers, younger than 18 years of age at the time of diagnosis and agreed (or their parents/legal guardians) to participate in the study. Participants are summoned to the follow-up clinic at predefined dates, starting one year after completion of anti-leukemic therapy.<sup>15</sup> These visits are repeated every two years until the age of 20 and at least 10 years after complete remission, and every four years thereafter. The program began in 2004 and relies on the constitution of a multicenter historical and prospective cohort, which includes both incident cases (diagnosed after the starting date of the participation of the center in the L.E.A. program) and prevalent cases (diagnosed between 01/01/1980 and the starting date of the participation of the center in the L.E.A. program).

Patients were eligible for the present study if they had been included in the L.E.A. program between 2004 and 2020, were female, were treated with HSCT after a MAC regimen, without menarche at the time of transplant and more than 18 years old at the time of last evaluation. Patients were excluded from the study if they underwent more than 2 HSCT. Among 186 women who fulfilled these inclusion/exclusion criteria, clinical and biological data were obtained in 178 and all these 178 women were included in the study group.

All patients (or their parents) provided written informed consent. This study was approved by the Sud Mediterranee V ethics committee (opinion n° 2012-A00984-39), in compliance with the General Data Protection Regulation.

### *Evaluation of the ovarian function after hematopoietic stem cell transplantation*

In the L.E.A. program, post-HSCT ovarian function evaluation was systematically proposed to all adolescents and women who had previously received HSCT. Typically, during the medical L.E.A. visits, hormone levels were tested and various clinical data were collected including spontaneous menarche/induction of puberty, puberty progress, sex steroid hormone replacement therapy (HRT), primary or secondary amenorrhea, pregnancy occurrence and outcome.

POI was defined by ESHRE as the association of an oligo/amenorrhea for at least 4 months, and an elevated FSH level  $> 25$  IU/l on two occasions at 4 weeks apart before the age of 40.<sup>4</sup> Spontaneous pregnancy was defined as a pregnancy obtained without any medically assisted reproductive procedure.

Depending on the level of damage to the ovarian reserve, three groups of ovarian hormonal status were distinguished. Girls who didn't have spontaneous menarche and needed HRT to induce puberty were classified as having immediate POI (IPOI). Girls who had spontaneous puberty and then presented a POI after a period of residual ovarian function were classified as having secondary POI (SPOI). Finally, women with neither clinical nor biological evidence of POI and without HRT at time of their last evaluation constituted the group without POI (noPOI).

Quality of Life (QoL) was evaluated with the SF-36 self-questionnaire (the Medical Outcome Study Short Form 36 Health Survey).<sup>16</sup>

Statistical methods are described in the supplemental data.

## RESULTS

### *Childhood hematopoietic stem cell transplantation survivors' characteristics*

We included 178 women from 15 L.E.A. centers. Their characteristics are summarized in Table 1.

The median age at HSCT was 7.7 [IQR25-75: 4.79-10.90] years old and the median age at last evaluation was 24.9 [21.08-30.1] years old. The median follow up duration since HSCT was 18 years [14.2-23.3].

In the studied cohort, 169 patients were treated with one HSCT and 9 were treated with two HSCT. Out of the 169 patients treated with one HSCT, 135 received an allogeneic and 34 an autologous HSCT. Among the 9 patients with two HSCT, 2 had autologous followed by allogeneic HSCT and 7 had 2 allogeneic HSCT.

Thirteen patients from the studied population had an ovarian tissue cryopreservation (OTC) before HSCT.

### *Conditioning regimen before hematopoietic stem cell transplantation*

Conditioning regimen depended on protocols in use at the time of HSCT, underlying diseases and their status, and history of previous CNS irradiation. All 178 women had received a MAC regimen, among which 116 had total-body irradiation (TBI) and 62 a Busulfan-based conditioning protocol (Table 1).

Most women prepared with TBI were treated with the commonly used French pre-transplant radiation regimen : they (107/116, 92%) received a total dose of 12 Gy divided in 6 fractions (i.e. 2 Gy twice daily during 3 days) with lung shielding at 8 Gy. Only 8 other women received a fractionated 10 to 11 Gy total dose and one a single 8 Gy dose. The cytostatic drugs used in association with TBI were: cyclophosphamide only in 53 patients, cyclophosphamide and fludarabine in 2, melphalan only in 3, cytarabine and melphalan in 50 and etoposide in 8 patients. Mean calculated cumulative alkylating dose per patient, using the cyclophosphamide equivalent dose (CED) was 4661 mg/m<sup>2</sup> (range: 0 to 15435).<sup>17</sup>

All 62 women who did not receive TBI were given busulfan (BU) at a myeloablative dose. BU was given per os or IV in 16 divided doses (4 doses per day for 4 days) at a total dose of 16 mg/kg or 480 mg/m<sup>2</sup> when given per os, and according to a previously published weight-based protocol when given IV. In addition to BU, patients also received cyclophosphamide (49 patients), melphalan (6 patients), aracytine and melphalan (5 patients) or fludarabine and thiotepa (2 patients). Mean cumulative CED dose was 9285 mg/m<sup>2</sup> (range: 5600 to 19 235).

### *Ovarian function after hematopoietic stem cell transplantation in leukemia survivors*

Out of the 178 included women, 106 (59.6%) needed an induction of puberty with HRT whereas 72 (40.4%) had spontaneous menarche. Among the 72 patients with spontaneous menarche, 33 developed POI secondarily and 39 women still had a residual ovarian function (Figure 1).

Table 2 resumes the mean FSH levels before introduction of HRT in the IPOI and SPOI groups and at last evaluation for the noPOI group (Table 2).

In the IPOI group, the median age for the introduction of HRT to induce puberty was 13.7 years [12.7-14.9] and the median age at last evaluation was 25.5 years [21.3-30].

In the SPOI group, the median age for spontaneous menarche was 13 years [11.9-14.1] , the median age for the introduction of HRT was 15.1 years [14.2-16.4] and the median age at last evaluation was 24.3 years [20.3-29.6].

In the noPOI group, the median age for spontaneous menarche was 12.7 years [12-13.5] and they still had spontaneous menstruations at 24.8 years [21.3-29.8].

Cumulative incidence of POI in women who had spontaneous menarche is shown in Figure 2. During the follow-up, among the 72 women of the cohort who had spontaneous menarche, 33 (45.8%) progressed to a POI. The cumulative incidence of POI occurrence increased rapidly affecting 40% of women within 5 years of having spontaneous menarche and more slowly thereafter, reaching 45% at 10 years (Figure 2).

***Risk factors for premature ovarian insufficiency in hematopoietic stem cell transplantation survivors***

Potential risk factors influencing ovarian function are analyzed in Table 3. There is a continuous effect of age at time of HSCT on ovarian status: using the median age and the quartile distribution of the cohort as a cut-off, older children at time of HSCT had a higher risk of developing POI. Indeed, more than 80% of the patients who underwent HSCT after the age of 10.9 years were in the IPOI group. In contrast, more than 65% of the patients who underwent HSCT before the age of 4.79 years had spontaneous menarche and almost 50% of them were in the noPOI group at last evaluation (Figure 3)

Thirteen patients from the study cohort had fertility preservation with OTC . Among them, 12 (92.3%) were in the IPOI group, one in the SPOI but none belonged to the noPOI group. OTC is a significant risk factor for POI. However, there was a statistically significant association between older age at first HSCT and history of OTC ( $p<0.001$ ), more than 90% of

women with history of OTC being older than 7.70 years old at HSCT (median age of the study cohort)(Table 3).

***Spontaneous pregnancy and outcomes in hematopoietic stem cell transplantation survivors***

Among the 178 women included in our cohort, 22 had at least one spontaneous pregnancy (12 %), with a total number of 37 spontaneous pregnancies leading to 17 live births, 14 miscarriages, 4 legal abortions and 2 therapeutic abortions.

Potential factors influencing the occurrence of spontaneous pregnancy in our study cohort are shown in Table 4. We observed a continuous effect of age at last evaluation on the occurrence of spontaneous pregnancies, older patients at last evaluation having higher probabilities of spontaneous pregnancy. Age at HSCT was not a prognostic factor, perhaps due to a statistically significant correlation between age at HSCT and age at last evaluation (Figure 4). Women from the noPOI group had a significantly better chance of spontaneous pregnancy than women in the IPOI and SPOI groups. Interestingly, none of those who had OTC enjoyed spontaneous pregnancy, although the difference did not reach the level of statistical significance (Table 4).

***Premature ovarian insufficiency and spontaneous pregnancies consequences on quality of life***

We compared the QoL profile in our study population with that of the French general population.<sup>18</sup> There was a highly statistically significant decline in the mental component

score of the study population, as well as for almost all subscales of SF-36 (additional Table 1A). However, we didn't find any statistically significant effect of the women's ovarian status or the occurrence of spontaneous pregnancy on their quality of life (additional Table 1B and 1C).

## DISCUSSION

We report the evolution of residual ovarian function and spontaneous pregnancies in 178 adult females treated before puberty for AL by HSCT prepared with a MAC regimen. Ovarian function after HSCT has been described in other studies but the survivors cohorts were often heterogeneous with various indications such as leukemia, Hodgkin lymphoma or severe aplastic anemia.<sup>7,19</sup> A strength of our study is to have included a large and homogeneous population of women, all treated before puberty for a similar pathology with similar treatments.

Temporary recovery of ovarian function has been previously described on prepubertal and midpubertal girls.<sup>11,13</sup> Based on these data, we chose to focus on girls who were prepubertal at the time of HSCT and had attained adulthood at last evaluation. Another significant strength of our study is its extended longitudinal follow up duration (median duration of 18 years after HSCT).

Several other studies which evaluated gonadal function after cancer treatment did not respond with a clear and uniform definition of ovarian impairment with, for example, heterogeneous thresholds of gonadotropin plasma levels.<sup>10,20</sup> Our study was based on the European Society of Human Reproduction and Embryology (ESHRE 2016), definition of POI.<sup>4</sup>

Moreover, some previous studies have reported pregnancies in cancer survivors after HSCT without specifying whether these were spontaneous or required assisted reproductive techniques such as oocytes donation.<sup>5,9</sup> In this study, we only report spontaneous pregnancies with a view to assess as accurately as possible residual ovarian function.

A number of risk factors have already been described regarding ovarian toxicity after MAC regimen for bone marrow transplantation. The age at HSCT is critical: POI is more frequent after HSCT in adult women, whereas in prepubertal girls, there is a higher probability of spontaneous menarche.<sup>5,10,11</sup>

Our data show that age at HSCT strongly influences residual ovarian function: more than 65% of patients who underwent HSCT before the age of 4.8 years had spontaneous menarche and almost 50% didn't have POI at last evaluation whereas more than 85% of patients who received HSCT after the age of 10.9 years didn't have spontaneous menarche and needed induction of puberty with HRT. Jadoul et al<sup>21</sup> observed that patients under the age of 10 at the time of HSCT for malignant and nonmalignant diseases showed significant and independently-associated higher rates of clinically proven persistent ovarian function. The protective effect of young age might be related to the higher number of NGFs in the ovarian reserve of younger girls. During the reproductive life, the decline in NGFs occurs in an exponential way.<sup>22</sup> We were surprised to observe a significantly increased chance of keeping functional ovaries when girls were treated before the age of 5 (48.8 %); Similarly, we report a gradual increase in the risk for POI with age at HSCT beginning much earlier than the previously described threshold of 10 years.

The identification of women endowed with residual ovarian function after HSCT and the timing until the definitive POI occurs remains a major challenge for counseling a long-term

fertility preservation strategy such as oocyte cryopreservation after puberty. According to our study, 40% of transplanted girls have spontaneous menarche but among them, 40% will progress to POI within 5 years of menarche, which is quite a short critical therapeutic window to consider fertility procedure.<sup>23</sup> Indeed, it could be discussed to perform an oocyte banking before definitive POI in these young adolescents as already described in case of risk of POI in women with a history of benign ovarian tumor and high risk of ovarian depletion.<sup>24</sup>

Infertility is a very frequent late effect after HSCT.<sup>25</sup> Pregnancy in transplanted women has been documented by Salooja et al. with a pregnancy rate of 0,6% (232/37362). This study included girls and adult women transplanted at different ages ranging from 6 to 36 with a median age at HSCT of 19 years.<sup>12</sup> The study of Diesch-Furlanetto et al. focused on pregnancies (naturally or by artificial insemination) both in childhood disease survivor transplanted women and partner pregnancies of childhood disease survivor transplanted males with a pregnancy rate of 0.7% (406/61047). The studied population included less than 30% of leukemia as HSCT indication.<sup>13</sup> Indeed, pregnancies after HSCT have been documented in several studies but with heterogeneous inclusion criteria : underlying diseases including malignant and non-malignant ones<sup>26,27</sup>; including patients transplanted at any age<sup>12</sup>; including men and women indifferently or without reporting whether the conception method was natural or involved medically assisted reproduction.<sup>5,13</sup>

To our knowledge, our study is the first one to assess spontaneous pregnancy in women who received HSCT at a prepubertal age. In the other cohort studies, the follow-up was too short to include pregnancies at ages for which family planning is considered. However, compared with the mean age of healthy women at their first child's birth (29 years old), our studied women delivered 5 years earlier (mean 24,3 years old).<sup>13</sup> With a median age at last evaluation of 24.9 years old, we probably underestimate the total number of pregnancies after HSCT.

We describe that more than 12% of women had spontaneous pregnancies. Surprisingly, we report more than 10% of legal abortions in these pregnancies with half of them in the IPOI group.

One of the main messages to highlight from this result is the absolute necessity to replace the HRT with a contraceptive method for the young adults to avoid non desired pregnancies, especially in girls with a history of induction of puberty.

Fertility impairment being such an important late effect after cancer treatment, fertility preservation procedures before treatment is one of the most important issue for survivor patients and for their quality of life.<sup>28</sup> OTC is the only option for fertility preservation in prepubertal girls. On the other hand, we observed an impairment of residual ovarian function in girls who have benefited from an OTC. In our study, only around 7% of the women had undergone an OTC before HSCT. OTC appears as a statistically significant risk factor for POI with more than 90% of these women being in the group IPOI. However, there is a potential age bias, because women who underwent OTC were older at time of HSCT and we previously described age at HSCT as an independent risk factor for POI. In addition, we did not describe any spontaneous pregnancy in women with a history of OTC. Consequently, we suggest that OTC before HSCT for AL might influence future ovarian function and fertility but this result must be confirmed in other cohorts because of the relatively small number of women and the potential age bias.

More than 200 live births after OTC and autotransplantation<sup>29,30</sup> have been reported worldwide, which gives OTC a rightful place in fertility preservation to patients of different ages<sup>31,32</sup> or treated for various diseases, especially non malignant ones.<sup>33</sup> In AL however, there is a concern about possible contamination of ovarian tissue by residual leukemic disease, which can potentially induce disease recurrence after ovarian autograft.<sup>34</sup> AL

remains a discussed indication for OTC.<sup>35,36</sup> One animal model study concluded that reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe.<sup>37</sup> Consequently, only a few women around the world have been transplanted after leukemia and this was done with maximal safety procedures to ensure that there was no residual disease in the graft.<sup>38-41</sup> Even for centers that do not consider autotransplantation of OTC in AL, OTC could be discussed in view of the emerging technology of in vitro folliculogenesis in human. To date, the “artificial ovary” technology has been successful in nonhuman animals, but not yet in humans.<sup>42,43</sup> Finally, the usefulness of OTC in young girls suffering from AL is questionable if ovarian tissue autograft couldn't be proposed. In the end, other studies assessing the potential impact of OTC on future ovarian function and fertility are needed to answer this important question.

Teinturier et al<sup>44</sup>, showed that unilateral oophorectomy in cancer survivors was associated with a 7-year earlier age at onset of menopause.

Several previous studies have documented an impairment of quality of life in childhood leukemia survivors.<sup>36,45-47</sup> Studies focusing on HSCT survivors also showed a decrease in their perceived QoL.<sup>48,49</sup> Our study showed significantly lower scores of QoL in HSCT survivors compared to the French general population especially on the mental component score. However, we were unable to detect an impact of the ovarian function status on QoL, perhaps because the impairment of QoL in these cases is multifactorial and might require a larger cohort to become visible.

Our study reported that spontaneous puberty and spontaneous pregnancies are possible and not so rare after HSCT. We evidenced a more resilient residual ovarian function especially when HSCT was performed before the age of 5. Age at HSCT remains a major risk factor for ovarian dysfunction with a continuous effect on ovarian function. It is important to identify

the therapeutic window of fertility preservation for those who had spontaneous menarche. As spontaneous pregnancies may occur, it is essential to propose contraceptive methods. More studies with a larger cohort of survivors are necessary to identify the potential impact of OTC on ovarian function in leukemia survivors who received HSCT during childhood.

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## TABLES

	Study patients <i>n</i> = 178	%
Age at diagnosis - median [IQ25-75]	5.88±3.8 [3.01-8.95]	
Age at HSCT – median [IQ25-75]	7.70±3.9 [4.79-10.90]	
Age at last evaluation – median [IQ25-75]	24.90±6.1[21.08-30.1]	
Leukemia type		
ALL	108	60.7
AML	70	39.3
Number of HSCT		
1	169	94.9
2	9	5.1
Type of HSCT n°1		
Autograft	36	20.2
Allograft	142	79.8
GvHD		
No	55	38.2
Yes	88	61.1
Sin data	1	0.7
MAC Regimen		
TBI-based	116	65.2
Radiation dose		
- 12 Gy (2 twice daily x 3 days)	107	92.2
- 10-11 Gy	8	6.9
- 8 Gy	1	0.9
Chemotherapy cumulative dose (CED, mg/m2)		
- Mean : 4661		
- Range : 0 to 15435		
Bu-based	62	34.8
Chemotherapy cumulative dose (CED, mg/m2 including BU dose)		
- Mean : 9285		
- Range : 5600 to 19235		
OTC before HSCT		
No	158	88.8
Yes	13	7.3
Sin data	7	3.9

*Table 1: Hematopoietic stem cell transplantations and survivors study population characteristics*

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; GvHD, graft vs host disease; BU, Busulfan; OTC, ovarian tissue cryopreservation. Ages are expressed in medians±standard deviation and quartiles.

	Ovarian status			<i>p</i>
	IPOI	SPOI	noPOI	
FSH (UI/L)	69.2±4.8	62.1±7.4	16.5±3	<.0001

*Table 2 : Mean FSH levels before introduction of HRT in the IPOI and SPOI group and at last evaluation for the noPOI group*

FSH levels are shown in UI/L with the mean± standard error

IPOI (Immediate Premature Ovarian Insufficiency); SPOI (Secondary Premature Ovarian Insufficiency); noPOI (without Premature Ovarian Insufficiency at last evaluation)

	Ovarian Status			p
	IPOI	SPOI	noPOI	
<b>Leukemia Type</b>				
ALL	58 (53.7)	24 (22.2)	26 (24.1)	0.128
AML	48 (68.6)	9 (12.9)	13 (18.5)	
<b>Number of HSCT</b>				
1	98 (58)	32 (18.9)	39 (23.1)	0.215
2	8 (88.9)	1 (11.1)	0 (0)	
<b>HSCT Type</b>				
Autograft	19 (55.9)	10 (29.4)	5 (14.7)	0.155
Allograft	87 (60.4)	23 (16)	34 (23.6)	
<b>GvHD</b>				
No	29 (52.7)	8 (14.6)	18 (32.7)	0.138
Yes	58 (65.9)	14 (15.9)	16 (18.2)	
<b>Conditioning regimen</b>				
BU	38 (61.2)	12 (19.4)	12 (19.4)	0.862
TBI	68 (58.6)	21 (18.1)	27 (23.3)	
<b>Age at leukemia diagnosis (years)</b>				
<= 3.01 (IQR 0-25)	17 (37.8)	10 (22.2)	18 (40)	<0.0001
3.02 - 5.88 (IQR 25-50)	20 (45.5)	11 (25)	13 (29.5)	
5.89 - 8.94 (IQR 50-75)	30 (66.7)	9 (20)	6 (13.3)	
>=8.95 (IQR 75-100)	39 (88.6)	3 (6.8)	2 (4.6)	
<b>Age at first HSCT (years)</b>				
<= 4.79 (IQR 0-25)	15 (33.3)	8 (17.8)	22 (48.9)	<0.0001
4.80 - 7.70 (IQR 25-50)	23 (52.3)	10 (22.7)	11 (25)	
7.71 - 10.89 (IQR 50-75)	30 (66.7)	10 (22.2)	5 (11.1)	
>= 10.90 (IQR 75-100)	38 (86.3)	5 (11.4)	1 (2.3)	
<b>Age at first HSCT (years)</b>				
<b>BU</b>				
<= 4.79 (IQR 0-25)	7 (29.1)	7 (29.1)	10 (41.8)	<0.01
4.80 - 7.70 (IQR 25-50)	9 (75)	2 (16.7)	1 (8.3)	
7.71 - 10.89 (IQR 50-75)	8 (80)	2 (20)	0 (0)	
>= 10.90 (IQR 75-100)	14 (87.6)	1 (6.2)	1 (6.2)	
<b>TBI</b>				
<= 4.79 (IQR 0-25)	8 (38.1)	1 (4.8)	12 (57.1)	<0.0001
4.80 - 7.70 (IQR 25-50)	14 (43.7)	8 (25)	10 (31.3)	
7.71 - 10.89 (IQR 50-75)	22 (62.8)	8 (22.9)	5 (14.3)	
>= 10.90 (IQR 75-100)	24 (85.7)	4 (14.3)	0 (0)	
<b>Age at last evaluation</b>				
<b>L.E.A. (years)</b>				
<= 21.08 (IQR 0-25)	21 (46.7)	14 (31.1)	10 (22.2)	0.325
21.09 - 24.90 (IQR 25-50)	28 (63.6)	6 (13.7)	10 (22.7)	
24.91 - 30.10 (IQR 50-75)	30 (68.2)	6 (13.6)	8 (18.2)	
>= 30.11 (IQR 75-100)	27 (60)	7 (15.6)	11 (24.4)	
<b>OTC</b>				
No	92 (58.2)	30 (19)	36 (22.8)	<0.05
Yes	12 (92.3)	1 (7.7)	0 (0)	

*Table 3: Evaluation of potential risk factors impacting ovarian status after hematopoietic stem cell transplantation for leukemia in childhood*

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; GvHD, graft vs host disease; BU, Busulfan; OTC, ovarian tissue cryopreservation

IPOI (Immediate Premature Ovarian Insufficiency); SPOI (Secondary Premature Ovarian Insufficiency); noPOI (without Premature Ovarian Insufficiency at last evaluation)

Ages are expressed in quartiles.

	Patients with spontaneous pregnancy		
	No	Yes	<i>p</i>
<b>Leukemia type</b>			
ALL	95 (88)	13 (12)	1.000
AML	61 (87.1)	9 (12.9)	
<b>Number of HSCT</b>			
1	147 (87)	22 (13)	0.604
2	9 (100)	0 (0)	
<b>HSCT Type</b>			
Autograft	28 (82.4)	6 (17.6)	0.382
Allograft	128 (88.9)	16 (11.1)	
<b>GvHD</b>			
No	49 (89.1)	6 (10.9)	1
Yes	79 (89.8)	9 (10.2)	
<b>Conditioning regimen</b>			
BU	55 (88.7)	7 (11.3)	0.816
TBI	101 (87.1)	15 (12.9)	
<b>Age at leukemia diagnosis</b>			
<= 3.01	39 (86.7)	6 (13.3)	0.989
3.02 - 5.88	39 (88.6)	5 (11.4)	
5.89 - 8.94	40 (88.9)	5 (11.1)	
>=8.95	38 (86.4)	6 (13.6)	
<b>Age at last evaluation (years)</b>			
<= 21.08	45 (100)	0 (0)	<0.001
21.09 - 24.90	39 (88.6)	5 (11.4)	
24.91 - 30.10	40 (90.9)	4 (9.1)	
>=30.11	32 (71.1)	13 (28.9)	
<b>Age at first HSCT (years)</b>			
<= 4.79	40 (88.9)	5 (11.1)	0.703
4.80 - 7.70	40 (90.9)	4 (9.1)	
7.71 - 10.89	37 (82.2)	8 (17.8)	
>= 10.90	39 (88.6)	5 (11.4)	
<b>Follow up duration from HSCT (years)</b>			
<= 14.34	44 (97.8)	1 (2.2)	<0.01
14.35 - 18.18	38 (86.4)	6 (13.6)	
18.19 - 23.56	42 (93.3)	3 (6.7)	
23.57+	32 (72.7)	12 (27.3)	
<b>OTC</b>			
No	136 (86.1)	22 (13.9)	0.22
Yes	13 (100)	0 (0)	
<b>Ovarian status</b>			
POI (IPOI&SPOI)	126 (90.6)	13 (9.4)	<0.05
noPOI	30 (76.9)	9 (23.1)	

*Table 4: Evaluation of potential factors influencing spontaneous pregnancy occurrence after hematopoietic stem cell transplantation for leukemia in childhood*

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; GvHD, graft vs host disease; BU, Busulfan; OTC, ovarian tissue cryopreservation; IPOI (Immediate Premature Ovarian Insufficiency); SPOI (Secondary Premature Ovarian Insufficiency); noPOI (without Premature Ovarian Insufficiency at last evaluation). Ages are expressed in quartiles.

**FIGURE LEGENDS**

*Figure 1: Ovarian function evolution of the survivors cohort after hematopoietic stem cell transplantation for leukemia before puberty*

In the studied cohort, of a total of 178 eligible survivors, 106 patients (59.6%) are in the group IPOI, 33 patients (18.5%) are in the SPOI group and 39 patients (21.9%) are in the group noPOI.

IPOI (Immediate Premature Ovarian Insufficiency); SPOI (Secondary Premature Ovarian Insufficiency); noPOI (without Premature Ovarian Insufficiency at last evaluation)

*Figure 2: Cumulative incidence of occurrence of premature ovarian insufficiency in women who had spontaneous menarche in the survivors cohort after hematopoietic stem cell transplantation for leukemia before puberty*

*Figure 3: Ovarian status depending on age at hematopoietic stem cell transplantation in the survivors cohort after hematopoietic stem cell transplantation for leukemia before puberty*

Variable ages are divided between quartiles of age (years):  $\leq 4.79$  (IQR 0-25); 4.80-7.70 (IQR 25-50); 7.71-10.89 (IQR 50-75);  $\geq 10.90$  (IQR 75-100).

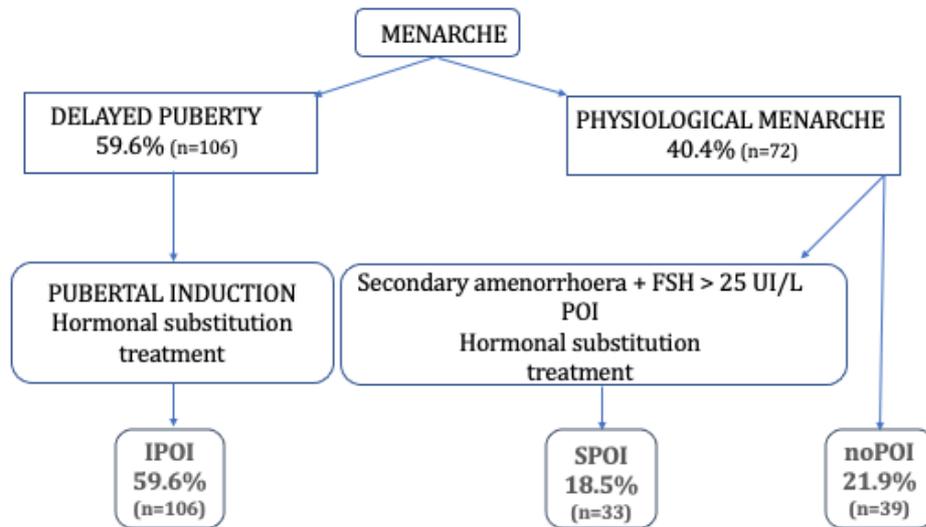
IPOI (Immediate Premature Ovarian Insufficiency); SPOI (Secondary Premature Ovarian Insufficiency); noPOI (without Premature Ovarian Insufficiency at last evaluation)

$p < 0.0001$

*Figure 4: Correlation between age at hematopoietic stem cell transplantation and age at last evaluation in the study cohort of leukemia women survivors*

HSCT, hematopoietic stem cell transplantation

## FIGURES

*Figure 1*

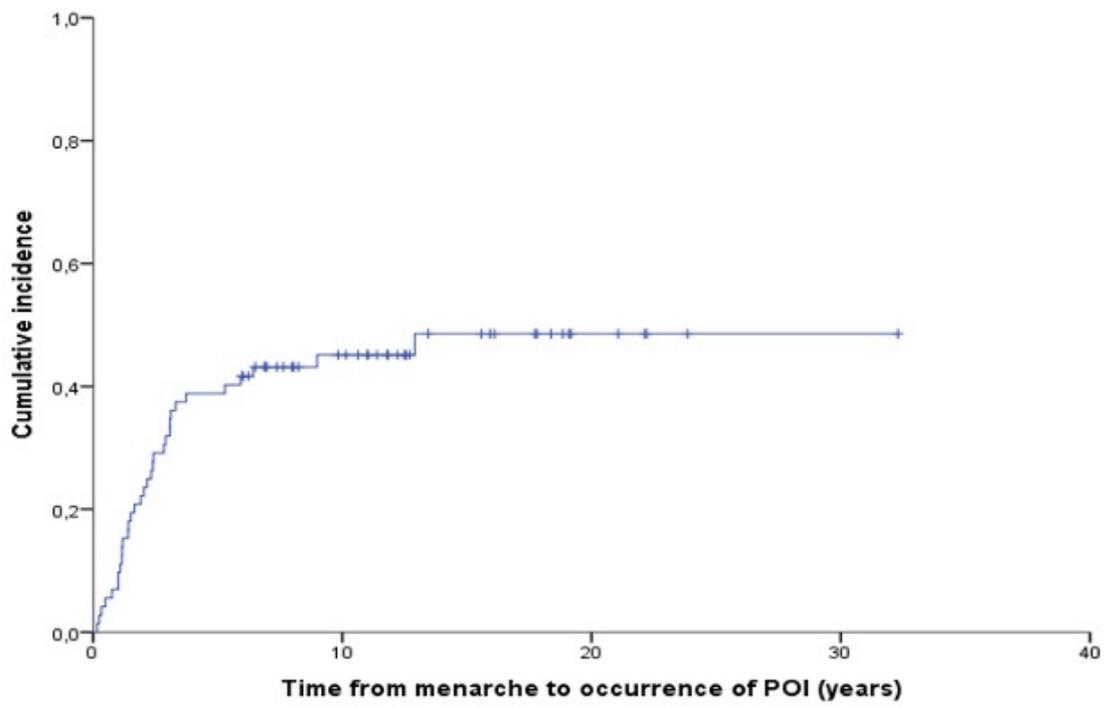


Figure 2

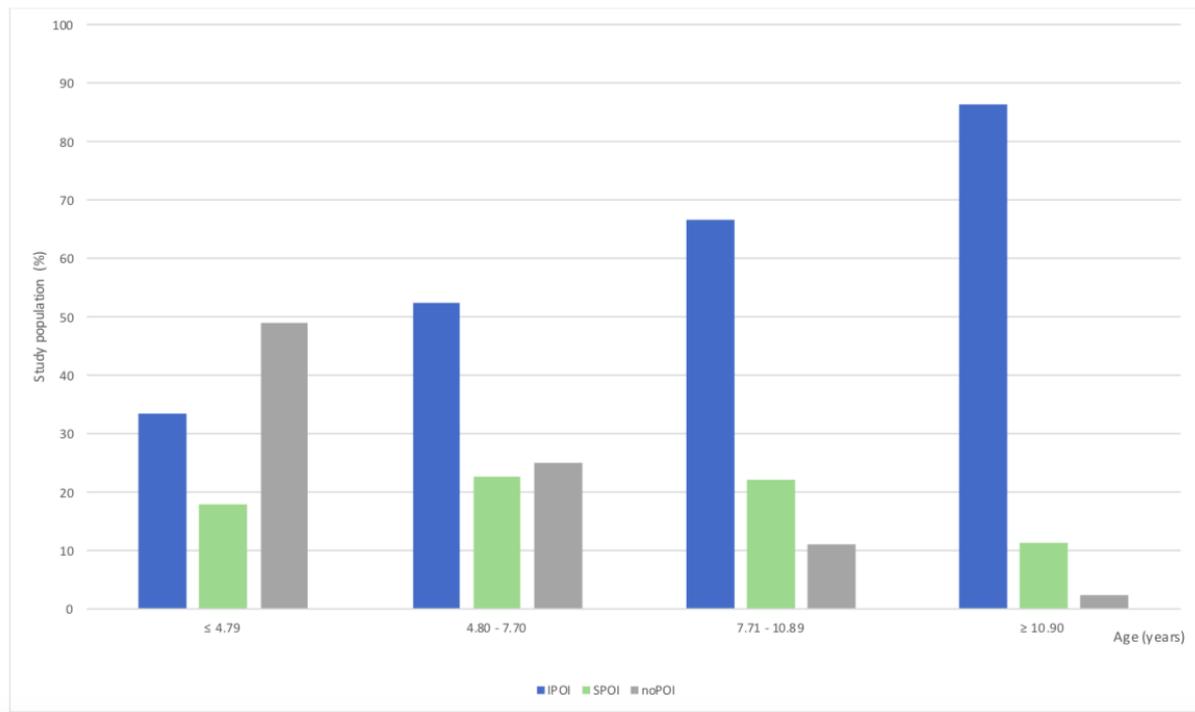


Figure 3

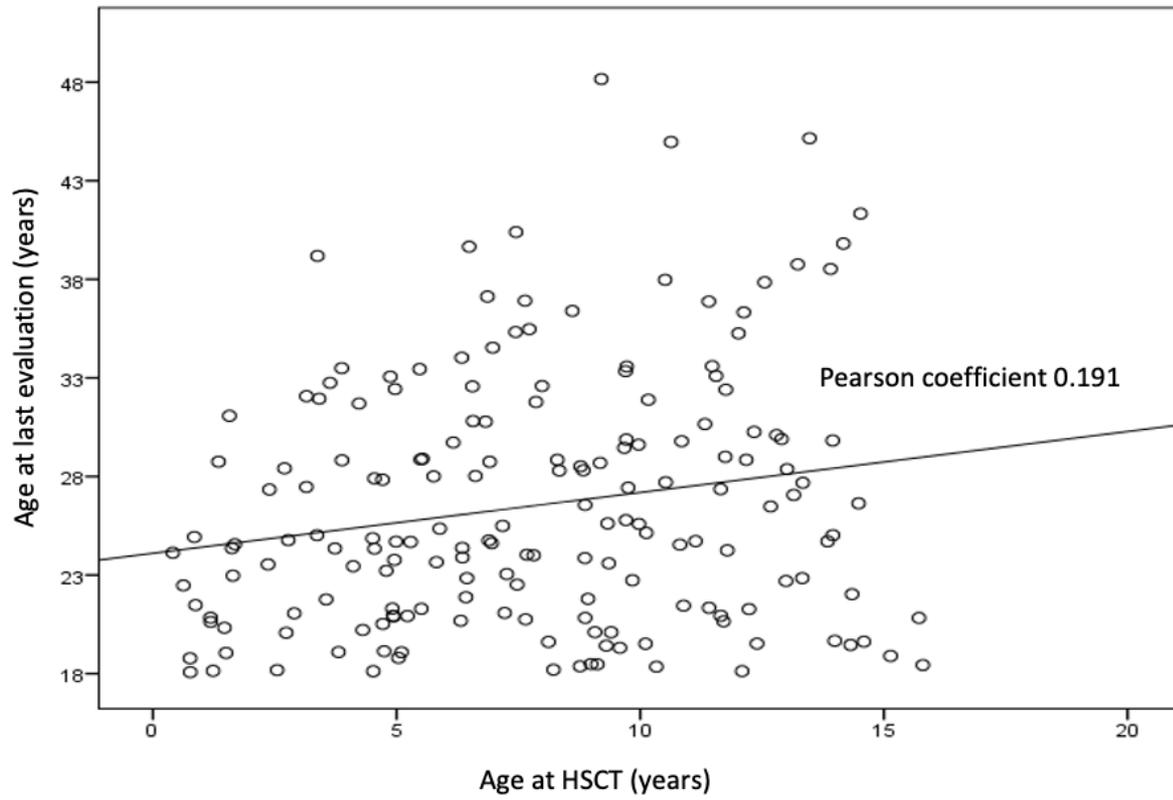


Figure 4

## SUPPLEMENTARY DATA

Quality of life (QoL) focusing on health was evaluated with the SF-36 self-questionnaire (the Medical Outcome Study Short Form 36 Health Survey), a widely used QoL measure that provides a non-disease-specific measure of adult functioning and well-being, allowing for comparison with a broad range of same-age norm groups.<sup>2,47,48</sup> SF36 includes 36 items describing eight dimensions. Two summary scores are also calculated from the subscales, a physical component score and a mental component score. All scores range between 0 and 100, with higher scores indicating better QoL.

### *Statistical analysis*

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Continuous age variables age at leukemia diagnosis, age at last evaluation and age at first HSCT-, were categorized into quartiles and shown as median [ IQR 25-IQR 75] in the main text. Qualitative data were expressed as percentages. Quantitative data were shown as mean±Standard Error of Mean (SEM). Chi2 and Fisher exact tests were used to compare qualitative variables. Quantitative variables were compared using the Student test or the Mann-Whitney test and ANOVA or Kruskal-Wallis test. A pairwise t-test with a Bonferroni correction was used to test the difference between each possible *pair* of means.

The SF 36 scores were compared according to ovarian function and spontaneous pregnancies in our study population. Quality of life scores were also compared with age- and sex-matched controls from the French population.

Cumulative incidence of occurrence of POI in women who had spontaneous menarche over time were estimated using the Kaplan-Meier method. The proportional hazards assumption was assessed *via* examination of the log-minus-log survival plot. For the analysis of cumulative incidence rates of occurrence of POI, patients were censored when there was no POI identified.

## ADDITIONAL TABLE

A	General population	Study population		
	M ±ES	N	M ±ES	p
Physical functioning	93.59 ±0.14	131	84.44 ±1.74	< 0.0001
Social functioning	81.22 ±0.15	129	68.02 ±2.3	< 0.0001
Role limitations due to physical health	88.1 ±0.15	126	79 ±2.21	< 0.0001
Role limitations due to emotional problems	83.64 ±0.19	128	66.18 ±1.7	< 0.0001
Emotional well-being	66.36 ±0.14	131	58.69 ±1.65	< 0.0001
Energy/fatigue	60.54 ±0.04	131	49.98 ±1.53	< 0.0001
Pain	79.52 ±0.08	129	69.88 ±2.34	< 0.0001
General health	73.26 ±0.14	131	55.16 ±1.98	< 0.0001
Physical component score	54.04 ±0.06	124	52.39 ±0.87	0.06
Mental component score	46.35 ±0.1	124	38.48 ±0.91	< 0.0001

B	IPOI		SPOI		noPOI		P
	N	M ±ES	N	M ±ES	N	M ±ES	
Physical functioning	85	83.77 ±2.1	23	84.57 ±4.62	32	88.11 ±3.08	0.560
Social functioning	83	68.07 ±2.81	23	69.57 ±5.26	32	71.48 ±4.8	0.815
Role limitations due to physical health	82	77.72 ±2.63	22	85.7 ±4.88	31	79.7 ±4.71	0.393
Role limitations due to emotional problems	83	64.26 ±2.02	22	70.83 ±4.13	32	68.62 ±3.38	0.255
Emotional well-being	85	58.4 ±2.14	23	59.13 ±3.61	32	62.03 ±3.43	0.661
Energy/fatigue	85	49.61 ±1.88	23	51.63 ±4.31	32	52.73 ±3.25	0.682
Pain	84	69.08 ±2.93	23	67.7 ±5.28	31	73.94 ±4.66	0.618
General health	84	55.32 ±2.39	23	51.61 ±5.04	32	60.75 ±4.2	0.314
Physical component score	79	52.3 ±1.05	22	52.5 ±2.11	31	53.23 ±1.77	0.900
Mental component score	79	38.12 ±1.15	22	39.42 ±2.02	31	40.21 ±1.85	0.594

C	Patients with spontaneous pregnancy				
	No		Yes		p
	N	M ±ES	N	M ±ES	
Physical functioning	119	84.48 ±1.79	21	87.25 ±4.09	0.547
Social functioning	117	68.8 ±2.35	21	70.83 ±6.18	0.740
Role limitations due to physical health	114	80.54 ±2.17	21	73.71 ±6.48	0.237
Role limitations due to emotional problems	116	65.45 ±1.74	21	71.23 ±4.09	0.195
Emotional well-being	119	58.6 ±1.75	21	63.57 ±4.23	0.275
Energy/fatigue	119	50.61 ±1.66	21	50.89 ±4.01	0.948
Pain	117	70.22 ±2.37	21	68.38 ±6.66	0.768
General health	118	55.92 ±2.09	21	56.14 ±5.09	0.967
Physical component score	111	52.93 ±0.87	21	50.55 ±2.41	0.293
Mental component score	111	38.33 ±0.95	21	41.42 ±2.25	0.198

*Additional Table 1:*

*A. Comparison of quality of life between the study population and the general French population with age and sex- matching*

- B. Comparison of quality of life of the study population depending on ovarian status*
- C. Comparison of quality of life of the study population depending on pregnancy outcome*