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Research Article

Pubertal and Fertility in Women from the French Childhood Leukemia Survivors' Cohort

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ABSTRACT

Objective: The aim of our study was to evaluate pubertal development and fertility outcomes in female survivors of childhood leukemia from the French Leucémie de l'Enfant et l'Adolescent (L.E.A.) cohort.

Methods: Data on puberty and fertility outcomes were collected during medical visits on preset dates. Since 2014, a more detailed assessment of fertility has been systematically offered to females aged >18 years *via* a self-reported fertility questionnaire.

Results: Of 992 women eligible for pubertal progression analysis, 491 were included for fertility evaluation. A higher prevalence of pubertal abnormalities was found after Hematopoietic Stem Cell Transplantation (HSCT). HSCT was associated with more use of Assisted Reproduction Technology (ART) (ORa=8.2(3.7-18.2), p<0.001). Even after first-line chemotherapy only, live births after ART were significantly higher than in the French general population (OR=2.8(1.3-6.1); p=0.02). In women who received HSCT compared to those who did not, there were significantly more children born after ART (ORa=97.9 (11.0-873.8)). The overall risk of preterm delivery was significantly greater than expected in the French general population (OR=3.0(1.8-4.9); p<0.001), even in women who received first-line

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chemotherapy only (OR=2.5(1.4-4.5), p=0.007). The overall incidence of babies weighting less than 2,500 g was significantly higher than expected (p=0.025). The standardized fertility ratio for the entire cohort was 0.5 (IQR=(0.3-0.6)) and significantly impacted by HSCT.

Conclusion: These data highlight the importance of providing information on prognosis, risks to fertility and ovarian function, counseling patients at the time of diagnosis and during the long-term follow-up of childhood cancer survivors in order to improve their quality of life.

Keywords: Childhood leukemia; Pubertal development; Fertility outcomes; Female survivors

Abbreviations: AL: Acute Leukemia; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloblastic Leukemia; ART: Assisted Reproduction Technology; BW: Birth Weight; cGvHD: chronic Graft *vs.* Host Disease; CNS: Central Nervous System; ENP: National Perinatal Registry; FGP: French General Population; FLCO: First-Line Chemotherapy Only; FQ: Fertility Questionnaire; HSCT: Hematopoietic Stem Cell Transplantation; INED: National Institute of Demographic Studies; INSEE: National Institute of Statistics and Economic Studies; IQR: InterQuartile Range; L.E.A: French Leucémie de l'Enfant et l'Adolescent; OR: Odds-Ratios; ORa: adjusted Odds-Ratios; QoL: Quality of Life; SFR: Standardized Fertility Ratio; TBI: Total Body Irradiation

INTRODUCTION

Continuing advances in childhood leukemia treatment mean that 80% of girls with Acute Lymphoblastic Leukemia (ALL) and 60% of those with Acute Myeloblastic Leukemia (AML) can now expect long-term survival following diagnosis [1,2]. This progress raises important questions concerning Quality of Life (QoL) and the risk of late effects after successful treatment. One of the greatest concerns associated with late effects is that of reproductive health, especially for young female survivors.

Ovaries are particularly sensitive to the adverse effects of cancer treatment because of the finite number of germ cells present in the postnatal ovary [3]. Ovarian damage resulting in impaired pubertal development and fertility have been described in childhood leukemia survivors [4,5]. Premature Ovarian Insufficiency (POI) and amenorrhea have often been used as the key outcomes in studies of reproductive function in women [6-8]. However, these outcomes may not fully reflect the experience of failure to conceive in these patients, who are additionally impacted by the social, psychological, and sexual effects of cancer and its treatment [9-11].

Fertility impairment and pregnancy complications in childhood cancer survivors have already been reported in large cohort studies such as the British Childhood Cancer Survivor Study in the United Kingdom and the Childhood Cancer Survivor Study in North America [12-16]. However, these studies concern different malignancies and often focus on "at risk treatment" (i.e., Radiotherapy and Hematopoietic Stem Cell Transplantation (HSCT)). In studies on girls with leukemia, most reports focus on heavily treated patients [17,18], and it remains unclear whether those who have received standard first-line leukemia treatment are also at risk of fertility deficits [7,19].

The aim of our study was to evaluate pubertal development and fertility outcomes in female survivors of childhood leukemia from the French Leucémie de l'Enfant et l'Adolescent (L.E.A.) cohort (NCT01756599), focusing on the risks of different therapies, particularly in women who have received only first-line chemotherapy treatment.

MATERIALS AND METHODS

The L.E.A. program was implemented in 2004 to prospectively evaluate the long-term status, Quality of Life and socioeconomic status of childhood Acute Leukemia (AL) survivors enrolled in treatment programs from January 1980 to the present in 16 cancer centers in France. The details of the program have already been described [20,21].

Briefly inclusion criteria were, age less than 18 at diagnosis; diagnosis of AL since January 1980; treatment (chemotherapy and/or transplant) carried out in one of the French pediatric cancer centers; surviving at the 24th month for grafted in first complete remission and at the 48th month for non-grafted. The date of diagnosis of AL is used as the reference date for calculating the deadlines for the evaluations. The data collection is done every 2 years except for patients over 20 years old, with a follow-up of more than 10 years from the diagnosis and having had no relapse during the previous 10 years for which the periodicity changes to 4 years.

Data on puberty and fertility outcomes were systematically collected during medical examination visits on preset dates, at their local sites. Moreover, since 2014, a more detailed assessment of fertility has been systematically offered to females aged >18 years *via* a self-reported fertility questionnaire.

The L.E.A. protocol was approved by the French National Program for Clinical Research (PHRC), the National Cancer Institute (NCI), and the review boards of the institutions involved. All the patients gave their written informed consent to take part in the study.

Early puberty was defined as beginning before the age of eight. Delayed puberty as a lack of breast development by age 13 or absence of menstruation by age 15. Early menopause was defined as one year without menstruation before the age of 45. For the description of pubertal abnormalities and ovarian insufficiency, the status "pubertal at diagnosis" or "pre-pubertal at diagnosis" was defined on the presence or absence of menstrual cycles.

Fertility was explored with pregnancy occurrence, outcome and live birth. Assisted Reproductive Technology (ART) included oocyte donation, sperm donation, intra-cytoplasmic sperm injection, frozen embryo transfer, intra-uterine insemination, and ovulation induction.

First-line chemotherapy was defined as chemotherapy treatment with no Central Nervous System (CNS) irradiation at any time in patients who never relapsed and never received HSCT. HSCT included autologous and allogeneic HSCT. The definition of CNS irradiation does not include TBI.

In Tables 1-3, because all patients did not answer all the

questions, we chose to express each data collected as the number of responses (numerators) depending on all the responses to the questions asked (denominators).

Statistical analyses were performed using Stata software version 15 (StataCorp, College Station, US). Continuous data were expressed according to the statistical distribution as mean and standard deviation or as median and interquartile range. The assumption of normality was assessed with the Shapiro-Wilk test.

The comparisons between groups (i.e., self-reported fertility questionnaire completed or not, relapse yes/no, HSCT yes/no, HSCT with TBI yes/no, chronic GvHD yes/no) concerning continuous variables such as maternal age at delivery, gestational age, and birth weight were performed using the Student t-test or, when the assumptions required for the t-test were not met, the Mann-Whitney test. The homoscedasticity was analyzed using the Fisher-Snedecor test. Categorical parameters were compared between groups using the Chi-square or Fisher's exact test. For data on puberty progression, the results were expressed as crude Odds-Ratios (OR) and 95% confidence intervals estimated using logistic regression. For comparisons concerning live-in relationship, child desire, and pregnancy intention and occurrence, the results were expressed as adjusted Odds-Ratios (ORa) and 95% confidence intervals estimated using multiple logistic regression with the following adjustment covariates- diagnosis, age at diagnosis and pubertal status at diagnosis. In order to evaluate the impact of treatments on the probability of being pregnant and live birth, multivariable logistic regression was conducted taking into account initial diagnosis, age at diagnosis, and decade of treatment ('80, '90, '00, '10) as adjustment covariates. The results were expressed as adjusted Odds-Ratios (ORa).

The age-specific fertility rate was calculated as the number of births per 100 women of a given age in a given year. The standardized fertility ratio was calculated as the number of actual births observed to the number that would be expected in women of the same age in the general population. Polynomial regression analysis was conducted to describe the time trend for the L.E.A. cohort women. For comparison with the metropolitan French general population, data from the National Institute of Statistics and Economic Studies (INSEE), the National Institute of Demographic Studies (INED), the National Perinatal Registry (ENP) were used [22-24]. The results concerning the age-specific fertility rate (continuous variable) were expressed as adjusted Interquartile Range (IQR).

All statistical tests were two-sided with the type-I error set at 5%. As analyses were exploratory, the individual p-values have been reported without applying mathematical correction according to several works reported in the literature, but specific attention was given to the magnitude of differences and to clinical relevance [25].

RESULTS

At the time of evaluation (2016), the total base L.E.A. cohort comprised 1,949 female leukemia survivors, of whom 992 were eligible (aged ≥ 18 years) and included for pubertal progression and fertility analysis. Of these, 612 (patients who were evaluated or re-evaluated between 2014 and 2016) were asked to participate in a detailed fertility evaluation by answering a self-reported fertility questionnaire; 491 women completed the questionnaire and were, therefore, included in the detailed fertility evaluation (Figure 1).

Of the 992 included patients, 839 (85%) had ALL, and 142 (14%) had AML. The mean follow-up duration from leukemia diagnosis to the last evaluation was 17 ± 6.6 years. Patients were treated according to the protocols in use at the time of AL diagnosis, depending on the leukemia subtype (AML or ALL) (i.e., FRALLE, EORTC, LAME, or ELAM). Most of the included patients received first-line chemotherapy only (n=738, i.e., 75%), 32 patients (3%) received CNS irradiation (18-24 gray), and 208 (21%) patients received at least one HSCT with (n=140, i.e., 14%) or without (n=68, i.e., 7%) Total Body Irradiation (TBI).

The women's characteristics used for the pubertal and fertility analysis (n=992) are summarized in Table 1. No significant difference was found between patients eligible and included for detailed fertility evaluation (n=491) and patients not included (n=501, i.e., 380 who were not invited to participate because they were evaluated before 2014 and 121 who were eligible but did not answer the self-reported fertility questionnaire) in terms of age and pubertal status at diagnosis, AL subtype, relapse ratio, and treatment modalities (p>0.05).

Puberty

Data on puberty progression are shown in Table 2. Abnormal progression of puberty occurred in 12% patients who were pre-pubertal at diagnosis (n=807) with, among them, significantly more delayed puberty (89%) than early puberty (11%). Primary amenorrhea was observed in 10% of pre-pubertal patients. In 18% of patients who were pubertal at diagnosis (n=178), permanent secondary amenorrhea was observed.

In 732 survivors (599 pre-pubertal and 133 pubertal at diagnosis) who received first-line chemotherapy only, primary amenorrhea occurred in 1%, secondary permanent amenorrhea occurred in 1.5%, and early menopause occurred in 0.4%, which is no different than observed in the French general population.

All these abnormalities were significantly less frequent in these patients than in the remaining 250 survivors (206 pre-pubertal and 44 pubertal at diagnosis), who received at least one other treatment (p<0.001).

Among 24 women who received CNS irradiation but not HSCT, we observed no abnormal progression of puberty, no primary or secondary amenorrhea and no early menopause (data not shown).

A higher prevalence of abnormalities was found in patients who received HSCT than in patients who did not, including primary amenorrhea (46% *vs.* 0.8%; OR=107.1(42.2-272.0)), secondary permanent amenorrhea (78% *vs.* 1.5%; OR=242.9(49.0-1203.7)), and early menopause (23% *vs.* 0.4%; OR=71.6(21.9-234.1)), p<0.001. In contrast, women who received HSCT with TBI were not significantly more at risk of developing abnormalities than females from the HSCT without TBI group.

The occurrence of post-transplantation cGvHD is a potentially devastating complication that can adversely affect pubertal development and post-pubertal ovarian function. This might in part explain the differences observed between the transplanted and non-transplanted groups. We explored this hypothesis in secondary analyses by dividing the transplanted group according to whether post-transplantation cGvHD occurred. Among transplanted survivors with cGvHD, no significantly higher prevalence of abnormalities was observed compared to those without cGvHD. There was only a slightly higher incidence of abnormal progression of puberty in the cGvHD group (p=0.049).

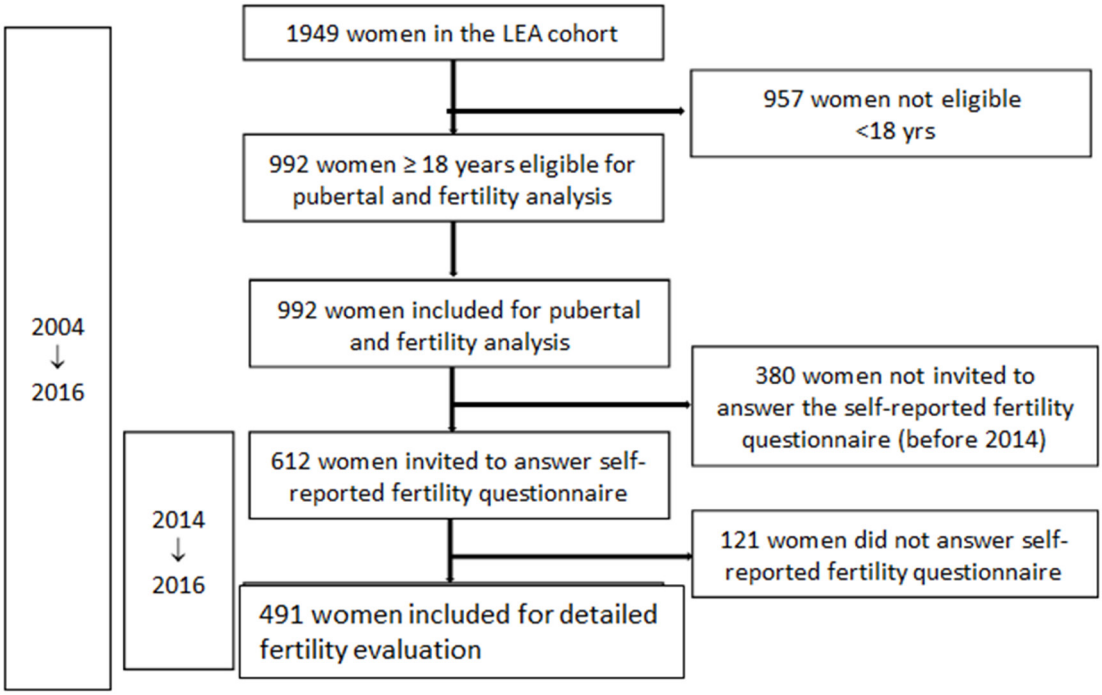

Figure 1: Flow chart of the pubertal and fertility study in LEA cohort.

Table 1: Characteristics of 992 female leukemia survivors aged ≥ 18 years.

		Medical book completed		
		Self-reported fertility questionnaire		
		Completed	Not completed	p-value**
Number of patients	992	491 (49.5%)	501 (50.5%)	
Age at evaluation (years)				
Median	25	25	25	
Range	18.0-46.5	18.0-46.5	18.0-43.2	
Initial diagnosis				
ALL	839/9929 (84.60%)	403/491 (82.10%)	436/501 (87%)	
AML	142/992 (14.30%)	82/491 (16.70%)	60/501 (12%)	
Others or unknown	11/992 (1.10%)	6/491 (1.20%)	5/501 (1%)	
Pubertal at diagnosis	178/985 (18.10%)	107/484 (22.10%)	71/501 (14.2%)	NS
First line treatment only*	755/988 (76.40%)	371/488 (76.00%)	384/500 (69.6%)	
Relapse	124/988 (12.60%)	60/488 (12.30%)	64/500 (12.8%)	
HSCT	208/990 (21.00%)	105/489 (21.50%)	103/501 (20.60%)	
With TBI	140/990 (14.10%)	70/489 (14.30%)	70/501 (14%)	
Without TBI	68/990 (6.90%)	35/489 (7.20%)	33/501 (6.6%)	
cGvHD	101/216 (46.80%)	49/110 (44.50%)	52/106 (49.1%)	
Thyroid dysfunction	138/426 (32.40%)	67/218 (30.70%)	71/208 (34.1%)	
≥ 1 pregnancy	227/867 (26.20%)	113/433 (26.10%)	114/434 (26.3%)	

Note: Disease; HSCT: Hematopoietic Stem Cell Transplantation; TBI: Total Body Irradiation.
*No-relapse and no-HSCT; **p-value for self-reported fertility questionnaire completed versus not-completed group'

Table 2: Pubertal abnormalities and ovarian insufficiency in 992 female leukaemia survivors.

Abnormalities	First-line chemotherapy only*			
	All patients	Yes	No	OR CI 95%
	n/N (%)	n/N (%)	n/N (%)	
Pre-pubertal at diagnosis	807/985(81.9)	599/732(81.8)	206/250(82.4)	-
Abnormal progression of puberty	94/797(11.8)	10/593(1.7)	84/203(41.4)	41.2(20.8-81.6)
Delayed puberty	81/794(10.2)	5/593(0.8)	76/200(38.0)	72.1(28.6-181.8)
Early puberty	10/794(1.3)	5/593(0.8)	5/200(2.5)	3(0.9-10.5)
Primary amenorrhea	81/790(10.3)	5/588(0.9)	76/201(37.8)	70.9(28.1-178.8)
Early menopause	31/747(4.1)	3/563(0.5)	28/183(15.3)	33.7(10.1-112.4)
Pubertal at diagnosis	178/985(18.1)	133/732(18.2)	44/250(17.6)	-
Secondary permanent amenorrhea	31/172(18.0)	2/130(1.5)	29/42(69.0)	142.8(30.5-667.5)
Early menopause	14/173(8.1)	0/133(0)	14/40(35.0)	NE
HSCT				
Pre-pubertal at diagnosis	807/985(81.9)	636/776(82.0)	169/207(81.6)	-
Abnormal progression of puberty	94/797(11.8)	12/630(1.9)	82/166(49.4)	50.3(26.3-96.0)
Delayed puberty	81/794(10.2)	5/630(0.8)	76/163(46.6)	109.(43.0-277.4)
Early puberty	10/794(1.3)	7/630(1.1)	3/163(1.8)	1.7(0.4-6.5)
Primary amenorrhea	81/790(10.3)	5/625(0.8)	76/164(46.3)	107.1(42.2-272.0)
Early menopause	31/747(4.1)	3/596(0.5)	28/150(18.7)	45.4(13.6-151.6)
Pubertal at diagnosis	178/985(18.1)	140/776(18.0)	38/207(18.4)	-
Secondary permanent amenorrhea	31/172(18.0)	2/136(1.5)	29/37(78.4)	242.9(49.0-1203.7)
Early menopause	14/173(8.1)	0/138(0)	14/35(40.0)	NE
HSCT with TBI				
Pre-pubertal at diagnosis	807/985(81.9)	56/67(83.6)	113/140(80.7)	-
Abnormal progression of puberty	94/797(11.8)	28/56(50.0)	54/110(49.1)	1(0.5-1.8)
Delayed puberty	81/794(10.2)	25/55(45.5)	51/108(47.2)	1.1(0.6-2.1)
Early puberty	10/794(1.3)	2/55(3.6)	1/108(0.9)	0.2(0.02-2.8)
Primary amenorrhea	81/790(10.3)	26/55(47.3)	50/109(45.9)	1(0.5-1.8)
Early menopause	31/747(4.1)	9/51(17.6)	19/99(19.2)	1.1(0.5-2.7)
Pubertal at diagnosis	178/985(18.1)	11/67(16.4)	27/140(19.3)	-
Secondary permanent amenorrhea	31/172(18.0)	10/11(90.9)	19/26(73.1)	0.03(0.01-0.09)
Early menopause	14/173(8.1)	5/10(50.0)	9/25(36.0)	0.6(0.1-2.5)

Note: HSCT: Hematopoietic Stem Cell Transplantation; TBI: Total Body Irradiation; NE: Not Evaluable; N: Number of patients with valid information; n: Number of patients who experienced the type of abnormality; OR: Odds Ratio; CI: Confidence Interval
*No central nervous system irradiation at any time, no HSCT and no relapse.

Pregnancy intention

Among the 491 women who completed the fertility questionnaire, 82% declared that they had already had sex and 46% that they had already been married or had a live-in relationship. The median age at the initiation of sexual activity was 17 years (Range: 13-27 years). No significant difference in time of sexual activity initiation was observed between women who received CNS irradiation and those who did not (p=0.96) or between survivors with cGvHD and those without it (p=0.19). However, this age was significantly higher in women who received HSCT in comparison to those who did not (18.2 *vs.* 17.6 years, p=0.03).

Fifty-two women (13%) had been trying to conceive for more than one year, and 8% declared that they had already used Assisted Reproduction Technology (ART). HSCT was associated with more use of ART (23% *vs.* 4%; ORa=8.2(3.7-18.2), p<0.001) (Table 3).

Thirty-one women (10%) had already thought about adoption. In the HSCT group, the idea of recourse to adoption was significantly more often declared (33% *vs.* 4%; ORa=14.5(5.9-35.8), p<0.001).

Three-hundred-and-sixty-four women had never been pregnant (76%). Of these, 10% declared that they wanted a child, 3% had already tried to conceive, and 7% had already thought about adoption. Among these women, desire for a child and pregnancy attempts were significantly more often stated by those who had received HSCT (20% *vs.* 6%, p=0.001 and 8% *vs.* 2%, p=0.03). Fourteen women declared unsuccessful ART, and nine of them had received HSCT (all with TBI).

Pregnancies

Among the 491 female survivors who completed the fertility questionnaire, 113 reported that they had already been pregnant. Of these 113 women, 82 (73%) were pre-pubertal at the time of diagnosis. These 113 women had had a total of 176 pregnancies (Table 3).

The probability of being pregnant was not significantly different between those who had received CNS irradiation and those who had not (44% *vs.* 23%, ORa=2.6(0.95-7.2), p=0.07), between those who received HSCT and those who did not (18% *vs.* 25%, ORa=1.5(0.9-2.7), p=0.139), and those who received TBI and those who did not (21% *vs.* 12%, ORa=0.5(0.2-1.6), p=0.24). In a multivariate analysis, no differences were observed between the four treatment groups with regard to the probability of being pregnant (Table 4).

Out of 176 pregnancies, 67 resulted in no live birth (38%) because of miscarriage, either spontaneous (n=33) or elective (n=25), stillbirth (n=2), early termination of tubal pregnancy (n=1), or unknown event (n=6).

The incidence of spontaneous abortion among all the female patients was 19%, similar to the reported incidence of 20% for the French general population (p=0.74). When HSCT recipients were considered, the incidence of 31% for spontaneous abortion was still not substantially higher than expected (p=0.2) and not substantially higher than observed among women treated without HSCT (15%; ORa=4.6(0.9-24.0), p=0.08). However, all the spontaneous abortions occurred in the TBI group.

There were 110 live births (including one set of twins) and 17 births (16%) after ART, which is significantly higher than in the French general population (3.1%, p<0.001). Even in survivors who received first-line chemotherapy only, 7/85 (8%) of live births were after ART, which is significantly higher than in the French general population (OR=2.8(1.3-6.1), p=0.02). Significantly more children were born after ART to women who received HSCT compared to those who did not (90% *vs.* 8%, ORa=97.9 (11.0-873.8)). On the other hand, 1/10 (10%) of live births in HSCT survivors were spontaneously conceived. In multivariate analysis, the occurrence of live birth was significantly higher in women who received first-line chemotherapy only in comparison to those who did not (p=0.029) and in women who did not receive HSCT in comparison to those who did (p=0.035) (Table 4).

Table 3: Live-in relationship, child desire, pregnancy intention and outcome and infant characteristics in 491 female leukemia survivors.

Characteristics	All patients	First-line chemotherapy only*		ORa CI 95%
		No	Yes	
	n/N (%)	n/N (%)	n/N (%)	
Ever had sex	389/477(81.6)	93/121(76.9)	294/354(83.1)	1.5(0.9-2.5)
Ever married or had a live-in relationship	215/468(45.9)	55/120(45.8)	159/346(46.0)	1.0(0.7-1.5)
Tried to be pregnant for ≥ 1 year	52/388(13.4)	23/97(23.7)	28/289(9.7)	0.4(0.2-0.6)
Ever used ART	34/432(7.9)	21/112(18.8)	13/319(4.0)	0.2(0.09-0.4)
Ever thought about adoption	31/320(9.7)	23/83(27.7)	8/237(3.4)	0.09(0.04-0.2)
Pregnancies	176	40	130	-
No live births	67/176(38.1)	19/40(47.5)	44/130(33.8)	0.3(0.04-1.4)
Spontaneous miscarriage	33/176(18.8)	10/40(25.0)	20/130(15.4)	0.4(0.08-1.6)
Medical interruption	2/176(1.1)	1/40(2.5)	1/130(0.8)	0.3(0.02-4.9)
Others**	32/176(18.2)	8/40(20.0)	23/130(17.7)	0.8(0.3-2.2)
Live births***	110/176(62.5)	21/40(52.5)	87/130(66.9)	4.09(0.7-22.4)

ART	17/110(15.5)	9/19(47.4)	7/85(8.2)	0.1(0.03-0.3)
Maternal age at delivery (years)				
Median (range)	26(17-37)	27(19-34)	26(17-37)	-
<30	84/104(80.8)	16/21(76.2)	66/81(81.5)	1.4(0.4-4.3)
Gestational age (weeks)				
Median (range)	39(26-41)	39(26-41)	39(31-41)	-
<37	19/90(21.1)	6/17(35.3)	13/71(18.3)	0.4(0.1-1.3)
Birth weight (g)				
Median (range)	3300(1000-5200)	3300(1000-3900)	3270(1970-5200)	-
<2500	12/109(11.0)	4/21(19.0)	8/86(9.3)	0.4(0.1-1.6)
LBW	10/12(83.3)	2/4(50.0)	8/8(100)	-
VLBW	2/12(16.7)	2/4(50.0)	0/8(0)	-
HSCT				
Ever had sex	389/477(81.6)	311/374(83.2)	76/101(75.2)	0.7(0.4-1.2)
Ever married or had a live-in relationship	215/468(45.9)	169/366(46.2)	45/100(45.0)	1.1(0.7-1.8)
Tried to be pregnant for ≥ 1 year	52/388(13.4)	29/305(9.5)	22/81(27.2)	4.2(2.1-8.5)
Ever used ART	34/432(7.9)	13/339(3.8)	21/92(22.8)	8.2(3.7-18.2)
Ever thought about adoption	31/320(9.7)	9/253(3.6)	22/67(32.8)	14.5(5.9-35.8)
Pregnancies	176	144	26	-
No live births	67/176(38.1)	49/144(34.0)	14/26(53.8)	6.1(0.8-47.2)
Spontaneous miscarriage	33/176(18.8)	22/144(15.3)	8/26(30.8)	4.6(0.9-24.0)
Medical interruption	2/176(1.1)	1/144(0.7)	1/26(3.8)	5.6(0.2-128.6)
Others**	32/176(18.2)	26/144(18.1)	5/26(19.2)	1.2(0.4-3.8)
Live births***	110/176(62.5)	96/144(66.7)	12/26(46.2)	0.2(0.02-1.3)
ART	17/110(15.5)	8/95(8.4)	9/10(90.0)	97.9(11.0-873.8)
Maternal age at delivery (years)				
Median (range)	26(17-37)	26(17-37)	28(19-34)	-
<30	84/104(80.8)	74/90(82.2)	8/12(66.7)	0.5(0.1-2.0)
Gestational age (weeks)				
Median (range)	39(26-41)	39(31-41)	38(26-41)	-
<37	19/90(21.1)	14/77(18.2)	5/11(45.5)	8.6(1.5-48.2)
Birth weight (g)				
Median (range)	3300(1000-5200)	3300(1970-5200)	3160(1000-3900)	-
<2500	12/109(11.0)	8/94(8.5)	4/12(33.3)	5.4(1.3–22.1)
LBW	10/12(83.3)	8/10(80.0)	2/10(20.0)	-
VLBW	2/12(16.7)	0/2(0)	2/2(100)	-
HSCT with TBI				
Ever had sex	389/477(81.6)	23/34(67.6)	53/67(79.1)	1.9(0.5-7.1)
Ever married or had a live-in relationship	215/468(45.9)	12/34(35.3)	33/66(50.0)	1.7(0.6-5.2)
Tried to be pregnant for ≥ 1 year	52/388(13.4)	5/27(18.5)	17/54(31.5)	2.0(0.5-8.2)

Ever used ART	34/432(7.9)	1/31(3.2)	20/61(32.8)	13.7(1.5-130.1)
Ever thought about adoption	31/320(9.7)	4/21(19.0)	18/46(39.1)	2.5(0.6-11.2)
Pregnancies	176	8	18	-
No live births	67/176(38.1)	3/8(37.5)	11/18(61.1)	1.5(0.03-581.3)
Spontaneous miscarriage	33/176(18.8)	0/8(0)	8/18(44.4)	NE
Medical interruption	2/176(1.1)	1/8(12.5)	0/18(0)	NE
Others**	32/176(18.2)	2/8(25.0)	3/18(37.5)	0.1(0.01-37.1)
Live births***	110/176(62.5)	5/8(62.5)	7/18(38.9)	0.7(0.01-256.4)
ART	17/110(15.5)	4/5(80.0)	5/5(100)	NE
Maternal age at delivery (years)				
Median (range)	26(17-37)	26(19-33)	29(22-34)	-
<30	84/104(80.8)	4/5(80.0)	4/7(57.1)	0.3(0.02–4.7)
Gestational age (weeks)				
Median (range)	39(26-41)	41(39-41)	36(26-39)	-
<37	19/90(21.1)	0/4(0)	5/7(71.4)	NE
Birth weight (g)				
Median (range)	3300(1000-5200)	3600(3220-3900)	2400(1000-3300)	-
<2500	12/109(11.0)	0/5(0)	4/7(57.1)	NE
LBW	10/12(83.3)	0/2(0)	2/2(100)	-
VLBW	2/12(16.7)	0/2(0)	2/2(100)	-

Note: ART: Assisted Reproductive Technology (including: *In vitro* fertilization, intra-cytoplasmic sperm injection, frozen embryo transfer, intrauterine insemination and ovulation induction); GA: Gestational Age; HSCT: Hematopoietic Stem Cell Transplantation; LBW: Low Birth Weight (1500 g to <2500 g); TBI: Total Body Irradiation; VLBW: Very Low Birth Weight (<1500 g)

N: number of patients with valid information; n: number of patients who experienced the type of abnormality; ORa: adjusted Odds Ratio; CI: Confidence Interval; NE: Not Evaluable

*No central nervous system irradiation at any time, no HSCT and no relapse; **Stillborn, ectopic pregnancy, on-going pregnancy, or abortion; ***One set of twins

Table 4: Multivariate analysis of potential factors influencing pregnancies and live births in 491 female survivors of childhood leukaemia according to initial diagnosis, age at diagnosis and decade of treatment.

Treatment	Pregnancy			Live births		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
First-line chemotherapy only*						
Yes	1	-	-	1	-	-
No	0.71	(0.40-1.24)	0.23	0.44	(0.21-0.92)	0.029
CNS irradiation						
No	1	-	-	1	-	-
Yes	1.26	(0.40-3.92)	0.69	0.74	(0.20-2.74)	0.66
HSCT						
No	1	-	-	1	-	-
Yes	0.64	(0.33-1.22)	0.17	0.39	(0.16-0.93)	0.035
TBI						
No	1	-	-	1	-	-
Yes	2.27	(0.47-11.1)	0.31	1.89	(0.21-16.9)	0.57

Note: CNS: Central Nervous System; HSCT: Hematopoietic Stem Cell Transplantation; TBI: Total Body Irradiation; CI: Confidence Interval; OR: Odds Ratio

*No CNS irradiation at any time, no HSCT, no relapse

The median gestational age at delivery was 39 weeks (Range: 26-41 weeks). The risk of preterm delivery among all female leukemia survivors (21%) compared with the French general population (8%) was significantly greater than expected (OR=3.0(1.8-4.9), p<0.001)). Even in women who received first-line chemotherapy only, the risk of preterm delivery was significantly greater (18%) than expected in the French general population (OR=2.5(1.4-4.5), p=0.007). We were not able to find any impact of CNS irradiation on preterm delivery. The risk of preterm delivery was more pronounced in the HSCT group (ORa=8.6(1.5-48.2), p=0.015), and all preterm deliveries occurred in the TBI group. To be noted that in the French general population, the percentage of low birth weight and preterm delivery in non-multiple pregnancies are comparable after ART or natural conception (in our data only one pregnancy was multiple).

Infants

A total of 110 infants were born. Of these, 71/90 (79%) were born after the gestational age of 37 weeks, and 97/109 (89%) had a birth weight >2,500 g.

The median birth weight at delivery was 3,300 g (Range: 1,000-5,200 g). The overall incidence of babies with a body weight less than 2,500 g was 11%, significantly higher than expected in the French general population (8.2%, p=0.025). We were not able to find any impact of CNS irradiation (when associated with first-line chemotherapy only) on birth weight. However, there were significantly more babies weighing<2,500 g in women who had received HSCT than in those who had not (33% *vs.* 9%; ORa=5.4,(1.3-22.1)).

Of 12 babies weighing<2500 g, 10 were Low Birth Weight (LBW) (between 1,800 and 2,400 g), and two were Very Low Birth Weight (VLBW) (between 800 g and 1,360 g); the latter were born from mothers who received HSCT with TBI.

Ten of the babies were small for their gestational age: Nine of the 96 live births by women treated with chemotherapy only and one of the 12 live births by women who received HSCT (with TBI). A set of twins born at 34 weeks had birth weights of 2,000 g and 3,000 g.

Age-specific fertility rate

As our cohort was relatively young, with 98% of the survivors younger than 40 years (i.e., still of childbearing age), the fertility rate can only be given as age-specific. The age-specific fertility rate estimations for the 992 female leukemia survivors from the L.E.A. cohort at the time of evaluation (2016) compared to the age-specific fertility rates in France in the same year are presented in Figure 2. The standardized fertility ratio for the entire cohort was 0.5 (IQR= (0.3-0.6)). It was significantly impacted by HSCT (0.1 (IQR= (0.0-0.4)), p<0.001) but not by pubertal status at diagnosis. To be noted that LBW was not associated with ART (p=0.07) but with pre-term delivery (p<0.001) data not show).

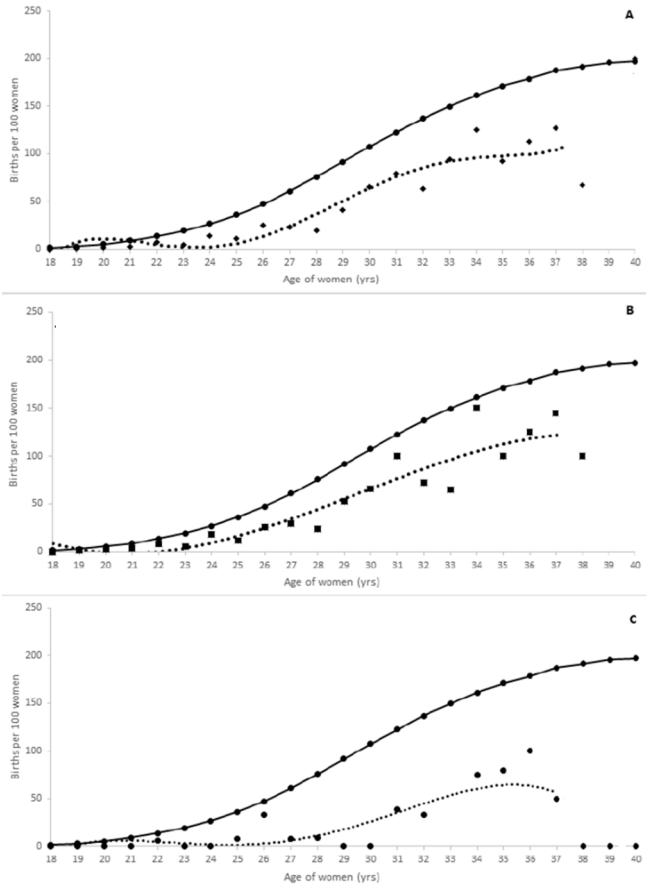

Figure 2: Age-specific fertility rates calculated as the number of births per 100 women of a given age in a given year estimated for 992 female leukaemia survivors (A) for 738 female leukaemia survivors after first-line chemotherapy only (B) for 208 female leukaemia survivors after HSCT (C) LEA cohort at the time of evaluation (2016) with a polynomial regression curb compared to age-specific fertility rates in France in the same year (data from the French National Institute of Statistics and Economic Studies (INSEE).

Note: (—•—): French general population (INSEE); (•): Leukemia survivors from LEA cohort (n=992); (▪): Leukemia survivors from LEA cohort after first-line chemotherapy (n=738); (•): Leukemia survivors from LEA cohort after HSCT (n=208)

DISCUSSIONS

Our study evaluated pubertal development and fertility outcomes in female survivors of childhood leukemia from the French Leucémie de l'Enfant et l'Adolescent (L.E.A-childhood and adolescent leukemia) cohort.

Our results showed no increased risk of pubertal or post-pubertal abnormalities in girls and women who received first-line chemotherapy only as compared with the French general population [26]. This is an important and reassuring finding. Moreover, none of the 24 women who received CNS irradiation but not HSCT showed any increased risk of pubertal or post pubertal abnormalities. This finding might suggest no impact of CNS irradiation on pubertal development but this inference should be made with caution because of the relatively small number of irradiated patients.

Like others [4,27-29], we found a clear impact of HSCT on pubertal progression and post-pubertal abnormalities (delayed puberty, primary amenorrhea, and early menopause). As previously reported by Bakker et al. almost 50% of pre-pubertal girls treated with TBI showed abnormal progression of puberty [30]. However, we found no marked differences between TBI and no-TBI groups. This may be due to the equivalent impact of high cumulative doses of alkylating agents on ovarian function in patients transplanted without TBI [8,28].

Age at initiation of sexual activity was no different in our cohort from the French general female population [23] or from the results reported by other authors [9]. However, it was significantly higher in women who received HSCT in comparison to those who did not (18.2 *vs.* 17.6 years, p=0.03).

Pui et al. evaluated long-term survivors of childhood acute lymphoblastic leukemia and showed that rates of marriage in a non-irradiated group were similar to the age- and sex-adjusted national averages. However, women in an irradiated group were less likely to be married [31]. In our study, we did not find any impact of different types of treatment on live-in relationship or marriage.

Van Dijk et al. reported no difference in the desire to have children between childhood cancer survivors and controls [32]. We found that the desire for a child and pregnancy attempt was more often reported by women who had had HSCT.

It was previously reported that diagnosis of leukemia was associated with consulting a fertility specialist (12%, OR=2(1-3)) [32]. In our cohort, 8% of patients declared that they had used ART, irrespective of the result. This rate is significantly higher than in the French general population (1%) (p<0.001). This is consistent with previous reports of an increase in the use of *in vitro* fertilization in female cancer patients compared with the general population [33] but contrasts with Barton et al.'s finding that, despite being equally likely to seek treatment for infertility, survivors were less likely to be prescribed medication for treatment of infertility than their siblings [34]. HSCT in our cohort was associated with significantly more recourse to ART and more unsuccessful ART.

Similar to Freycon et al. who reported that TBI and alkylating agents were negatively correlated with fecundity-with a standardized fertility ratio of 0.62 in patients treated with chemotherapy only *vs.* 0.17 in patients who received TBI conditioning allografts [19] we found a significant decrease in age-specific fertility rate in our patients impacted by HSCT. Also similar to findings by Freycon et al. [19], maternal age in our cohort was younger than in the French general population, but this may be merely artefactual owing to the young age of our cohort.

The incidence of no live birth in our survivors treated with first-line chemotherapy only (34%) was consistent with that previously reported in female AML survivors [7]. However, in patients who had received HSCT, the incidence in our cohort (54%) was higher than that found by Sanders (28%) [17]. Concerning the spontaneous abortions, the overall incidence in our cohort was 19%, reassuringly no higher than in the French general population [24]. The incidence in patients treated with first-line chemotherapy only was 15%, less than previously reported [7]. Concerning our female survivors who had received HSCT with TBI, the incidence of spontaneous abortion (44%) was consistent with the figures of Sanders et al. [17].

Sixteen percent of the born babies in our study were conceived after ART, significantly higher than in the French general population (3.1%) [22], with a significantly higher incidence in women who had received HSCT (90%, ORa=97.9(11.0-873.8)).

Although the risk of premature delivery and delivery of low birth weight offspring in survivors of childhood cancer has been previously reported [12-16], few studies have focused particularly on childhood leukemia survivors and on the impact of different treatment [7,13,14,17].

We found that in our leukemia survivors, the incidence of preterm delivery was significantly higher (21%) than in the French general population (8%). It was higher than expected even in women treated with first-line chemotherapy only (18%). Our findings are consistent with those of Mueller et al., who found OR=2.6(1.8-3.6) for preterm delivery [14], and Signorello et al. who found the rate of preterm births was 19% [13]. Our results differ, however, from Molgaard-Hansen et al.'s findings that all babies born at term in leukemia survivors who had been treated by chemotherapy only [7]. In our cohort, we failed to find any substantial difference in the incidence of preterm delivery in patients who received HSCT with or without TBI [17].

In our leukemia survivors, the incidence of LBW babies was significantly higher (11%) than in the French general population (8%) [22], which is consistent with previous reports [14], except for women treated with first-line chemotherapy only (9%). The increased incidence of LBW babies born from HSCT survivors in our cohort was similar to that reported by Sanders et al. [17].

One of the limitations of our study that must be considered is that current participating centers do not cover the entire country, although the cohort represents a geographical coverage of three-quarters of French pediatric onco-hematology centers. As far as the evaluation of fertility is concerned, the principal weakness is the young age of our survivors: 98% were younger than 40 years old, and 81% were younger than the median maternal age (30.4 years) in the French general population [22-24].

The main strength of our study is the size of this relatively homogenous cohort, even if some heterogeneity of treatments from the eighties until now may be a confounding factor.

CONCLUSION

In female survivors of childhood leukemia who received first-line chemotherapy only, the occurrence of pre and post pubertal abnormalities is not different than expected in the French general population. However, their fertility is impacted as they showed more use of ART and more risk of preterm delivery.

We confirmed that those who have relapsed or received HSCT have more frequently impaired pubertal development and fertility, but we failed to show any impact of CNS irradiation or TBI. In all treatment groups, the standardized fertility ratio was lower than expected. These data highlight the importance of providing information on prognosis, risks to fertility and ovarian function, counseling patients at the time of diagnosis and during the long-term follow-up of childhood cancer survivors in order to improve their quality of life.

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AUTHOR CONTRIBUTIONS

Writing original draft preparation was done by Victoria Grèze and Justyna Kanold, supervision was performed by Justyna Kanold. Foundation of the French Childhood Cancer Survivor Study for Leukemia (L.E.A. cohort) was done by Gérard Michel and Pascal Auquier. Data analysis was performed by Bruno Pereira. Local investigation was done by Nadège Rouel. All the other authors are co-investigators and collected data in their different French centers, they all agreed to the published version of the manuscript.

DATA AVALIBILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL

The French Leucémie de l'Enfant et l'Adolescent (L.E.A.) cohort has been approved (NCT01756599).

CONSENT TO PARTICIPATE

Written informed consent was obtained from the parents.

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