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SURVIVORSHIP: RESEARCH ARTICLE

Female reproductive function after treatment of childhood acute lymphoblastic leukemia

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Abstract

Background: The aim was to evaluate self-reported reproductive characteristics and markers of ovarian function in a nationwide cohort of female survivors of childhood acute lymphoblastic leukemia (ALL), because prior investigations have produced conflicting data.

Procedure: Self-reported reproductive characteristics were assessed by questionnaire among 357 adult 5-year survivors, treated between 1964 and 2002, and 836 controls. Ovarian function was assessed by serum levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and inhibin B and by antral follicle count (AFC). Differences between controls and (subgroups of) survivors (total group, chemotherapy [CT]-only group, CT and radiotherapy [RT] group) were analyzed.

Results: Survivors treated with CT only do not differ from controls regarding timing of menarche, virginity status, desire for children, or pregnancy rates. Compared to controls, the CT+RT group was at significantly increased risk of a younger age at menarche ($P < .01$), virginity, an absent desire for children, and lower pregnancy rates (odds ratio [OR] [95% CI]: 0.3 [CI 0.1-0.6], 0.5 [0.3-0.9], and 0.4 [0.2-0.9], respectively). Survivors in the CT-only group were significantly younger at the birth of their first child. Pregnancy outcomes were not significantly different between any (sub)groups. Survivors treated with total body irradiation (TBI) or hematopoietic stem cell transplantation (HSCT) are at increased risk of abnormal markers of ovarian function.

Conclusion: Reproductive function of ALL survivors treated with CT only does not differ from controls. However, survivors additionally treated with RT seem to be at an

Abbreviations: AFC, antral follicle count; ALL, acute lymphoblastic leukemia; AMH, anti-Müllerian hormone; CED, cyclophosphamide equivalent dose; CT, chemotherapy; DCOG, Dutch Childhood Oncology Group; FSH, follicle-stimulating hormone; HC, hormonal contraceptive; HSCT, hematopoietic stem cell transplantation; LPD, luteal phase deficiency; OR, odds ratio; RT, radiotherapy; SD, standard deviation; TBI, total body irradiation.

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increased risk of certain adverse reproductive outcomes. Providing personalized counseling about (future) reproductive health risks in this group is imperative.

KEYWORDS
acute lymphoblastic leukemia, childhood cancer survivors, fertility, pediatric cancer, pregnancy outcomes, reproductive function

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer. Fortunately, improved stratification and treatment strategies have improved 5-year survival rates beyond 90% for ALL patients in developed countries.[1–3] As an increasing number of patients survive to reach an age at which they consider parenthood, there is a growing need for information regarding the potential effects of treatment on reproductive function among both patients with ALL and survivors.

Although treatment-related fertility deficits are known to occur following treatment of childhood cancer,[4–8] fertility studies limited to ALL survivors are scarce and show conflicting results. In some studies, pregnancy or birth rates among childhood ALL survivors were found to be similar compared to the general population,[9,10] while in other studies these rates were significantly reduced among childhood ALL survivors compared to the general population.[11–14] In one of these studies, fertility deficits disappeared after correction for marital or cohabitation status,[13] a fertility-associated factor known to be reduced among ALL survivors.[12,13,15] In another study, additional correction for marital cohabitation status did not change the association with fertility deficits.[11] Survivors previously treated with cranio(spinal) radiotherapy (RT), however, have consistently shown to be at risk for lower birth rates compared to both survivors not treated with RT [12] or general population controls.[9,11,14]

With regard to prevalence and risk factors of adverse pregnancy outcomes, only Green et al[16] have evaluated the risk of miscarriage specifically among ALL survivors. Those treated with craniospinal RT were at increased risk compared to ALL survivors not treated with RT. No previous studies have compared rates of (other) adverse pregnancy outcomes among survivors of childhood ALL to those in the general population in full nationwide cohorts.

Hormonal and ultrasound markers (anti-Mullerian hormone [AMH], follicle-stimulating hormone [FSH], inhibin B, and antral follicle count [AFC]) are also useful in assessing treatment-related ovarian damage. Abnormal values may indicate decreased ovarian function, which may lead to a limited reproductive window with subsequent reduced pregnancy rates.[8]

However, studies examining markers of ovarian reserve among survivors of childhood ALL are few and also provide contradictory evidence. Survivors of ALL treated according to high-risk protocols were found to have low AMH levels compared to controls.[17] Furthermore, low AMH levels have been reported in 26% of long-term ALL survivors.[18] In contrast, results of another study showed that AMH levels of long-term ALL survivors treated with cranial RT were similar to those of both controls and survivors not treated with radiotherapy.[19] Studies evaluating AFC in a large cohort of childhood ALL survivors have not been performed to date.

As the existing evidence is contradictory, more evidence-based knowledge is needed in order to adequately address fertility-related concerns of female survivors of childhood ALL, and to clarify the possible risks of subfertility, infertility, and adverse pregnancy outcomes.

The primary aim of this study was to evaluate pregnancy rates and ovarian function in a large national cohort of female survivors of childhood ALL using both self-reported data and clinical markers. In addition, we aimed to evaluate other self-reported reproductive characteristics, that is, occurrence of menarche, virginity status, desire to have children, first pregnancy outcomes, and occurrence of a premature menopause.

2 | METHODS

2.1 | Study design and study population

This study is part of the Dutch Childhood Oncology Group (DCOG) LATER-VEVO study, a nationwide retrospective cohort study investigating the effects of childhood cancer treatment on reproductive function, ovarian reserve, premature menopause, and pregnancy outcomes in female survivors.[8,20] Detailed information regarding the inclusion criteria, exclusion criteria, other study characteristics, and comparisons between both types of controls have been described elsewhere.[8,20,21] In total, 1106 female childhood cancer survivors and 836 controls participated in the VEVO study. For the current study, we included only those survivors treated according to one of the DCOG ALL protocols.[22–24]

2.2 | Data collection and outcome definition

Data were collected by questionnaire, blood sampling, and a transvaginal ultrasound of the reproductive organs. Survivors could participate in one or all parts of the study.[20]

2.2.1 | Questionnaire data

Self-reported data used for the current study from the DCOG LATER-VEVO questionnaire, an adaption of a previously well-tested questionnaire,[25,26] were: age at time of study, marital and cohabitation status, age at menarche, having had sexual intercourse, use of hormonal medication, having (had) a desire for children, ever having been pregnant, the number of biological children, time to pregnancy, age at birth of first child, (adverse) pregnancy outcomes, menopausal status, age at menopause, educational level, weight, and height.

Data on time to pregnancy, defined as number of months of unprotected sexual intercourse until pregnancy, were collected from women who had achieved a pregnancy. Pregnancy outcomes included a live or stillbirth, miscarriage, or abortion. A pregnancy ending before gestational week 20 was considered a miscarriage, while a pregnancy ending with the death of the foetus in gestational week 20 or later was defined as a stillbirth. A live birth delivery occurring before gestational week 37 was defined as a preterm delivery. For the evaluation of pregnancy outcomes, only data on first pregnancies were used. Desire to have children was evaluated as having a "current or future desire" as well as "ever" having had a desire. Participants with biological children or who were pregnant at time of study and indicated not to have a current or future desire for additional children, were defined as "ever" having had a desire for children. Menopause was defined as the absence of menses for at least 12 consecutive months (not due to pregnancy, breast feeding, or use of contraceptives). In addition, women who reported to use hormone replacement therapy at time of study were also considered menopausal. Premature menopause was defined as menopause before the age of 40 years.

2.2.2 | Hormonal and ultrasound markers of ovarian function

Levels of FSH, AMH, and inhibin B were evaluated from collected serum samples, while AFC, defined as the number of antral follicles sized 2-10 mm in both ovaries, was determined by transvaginal ultrasound. All hormonal and ultrasound measurements were performed on cycle day 2-5 of a natural menstrual cycle or randomly in case of amenorrhea (no menses >6 months). Women on hormonal contraceptives (HCs) were asked to discontinue HC use at least 2 months prior to the study measurement. Those not discontinuing HCs were measured on day 7 of the HC-free week. Women who reported using a hormone-releasing intrauterine device, long-acting contraceptive injections, or women with a contraceptive implant were excluded from the clinical measurement. Additionally, women who had undergone previous ovarian surgery or hysterectomy or who were aged ≥52 years at time of study were excluded from the analyses. Ultrasound measurements were performed by trained personnel and three-dimensional images of the ovaries were stored, enabling retrospective AFC assessment by one assessor at a later time.

2.2.3 | Data on diagnosis and treatment

Details on prior cancer diagnosis and treatments (given for initial malignancy, recurrences, and any known new primary malignancies until time of study) were collected from original medical files and DCOG registry and entered into an electronic database. For nonparticipating survivors and survivors who died after surviving for at least 5 years, data on diagnosis, treatment received, attained age, and age at diagnosis were also collected. All included patients were treated with chemotherapeutic agents, with or without central nervous system-directed RT. Myeloablative transplant conditioning regimens, prior to allogeneic hematopoietic stem cell transplantation (HSCT), often include total body irradiation (TBI) in combination with alkylating agents. In order to quantify the total alkylating agent exposure of the survivors, the cyclophosphamide equivalent dose (CED) score was calculated.[27]

2.3 | Statistical analysis

For the current study, data of several participant groups were compared. First, all survivors of ALL were compared with controls. Furthermore, the total survivor group was divided into two subgroups: survivors treated with chemotherapy only (CT-only group) and survivors treated with CT and RT (CT+RT group). Subjects in these two subgroups were compared with controls and with each other, thereby evaluating potential treatment-related differences. We performed

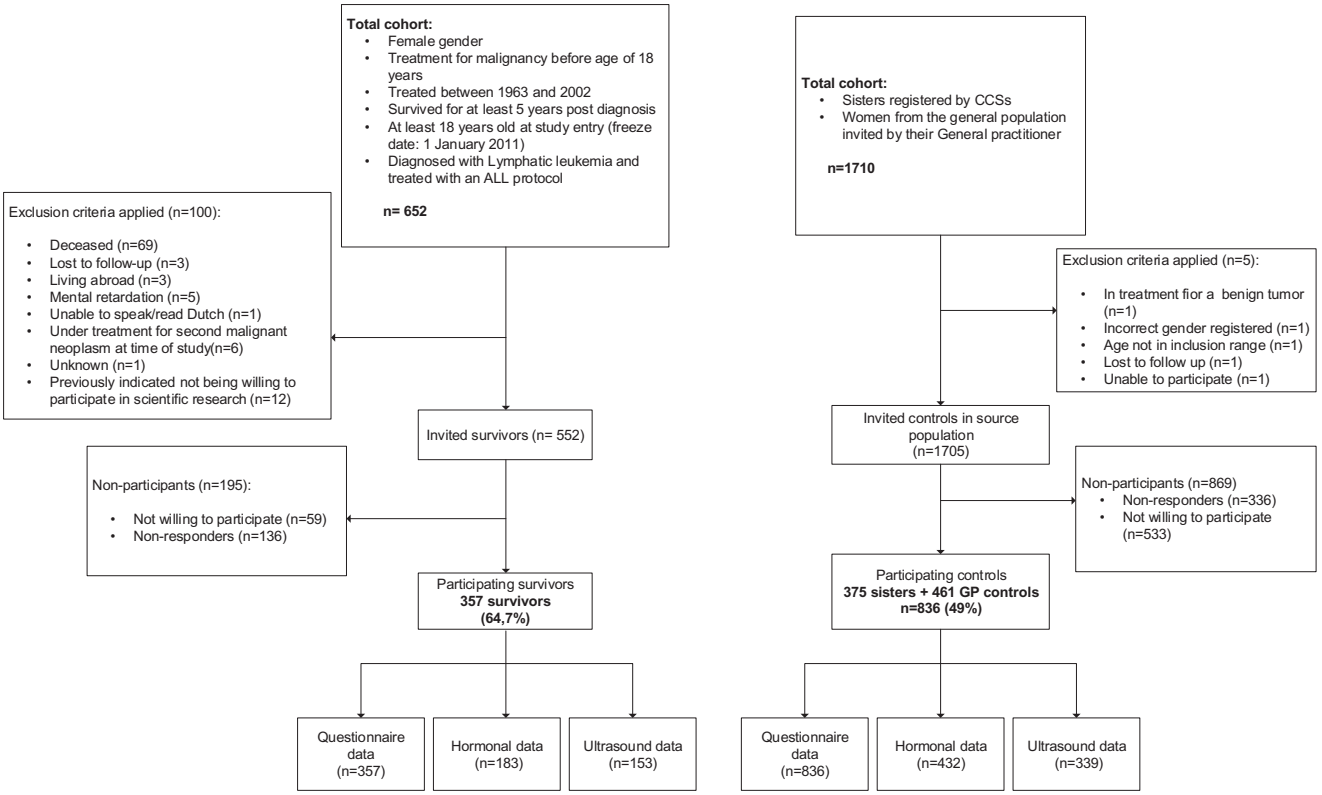

FIGURE 1 Flow chart of survivors (left) and controls (right) invited for the study

analyses excluding survivors treated with TBI as conditioning regimen for HSCT. Additionally, we also performed analyses excluding survivors treated with any kind of conditioning regimen prior to HSCT.

Differences between basic characteristics of the participant groups were analyzed using the chi-square tests, Student *t*-tests, or Mann-Whitney U tests, where appropriate. Self-reported outcomes of participant groups were compared by either linear or logistic regression analyses. All analyses were corrected for age at time of study, educational level, and marital status, unless specified otherwise.

Pregnancy rates and the probability of achieving a pregnancy were calculated only among those study participants who ever pursued a pregnancy. Women were identified as being "at risk" of pregnancy if they ever had the intention to become pregnant. Hence, women who had never had sexual intercourse and those who indicated never having tried to become pregnant in the past were excluded. In addition, women who had been pregnant once and terminated this pregnancy by means of an induced abortion were also excluded in order to avoid bias.

Data on hormonal markers were dichotomized (abnormal hormonal levels yes or no) prior to analysis. Low AMH and low AFC were defined using age-specific cut-off values, that is 2 SD (standard deviation) below the mean value of the control subjects within the concerning age group.[8] Elevated FSH and low inhibin B were defined using fixed cut-off values (ie, ≥10 U/L and <20 ng/L, respectively).[8] Hormonal and ultrasound data were compared using logistic regression analysis, with results being corrected for age at time of study, hormonal use, and BMI at time of study.

All analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows. A two-sided *P*-value of <.05 was considered statistically significant.

3 | RESULTS

Of all 547 eligible ALL survivors in the DCOG LATER-VEVO cohort and 1705 eligible controls, 357 survivors (64.7%) and 836 controls (49%) agreed to participate in this study (Figure 1). Roughly half of the participants provided blood samples (n = 183 survivors [51.3%] and n = 432 controls [51.7%]), whereas transvaginal ultrasound data were available for 153 survivors (42.9%) and 339 controls (40.6%). Table 1 depicts the demographic characteristics of the two main participant groups (total survivor group and controls) and the two subgroups within the total survivor group (the CT-only group and the CT+RT group).

Survivors in the total group as well as in the CT-only group were significantly younger than controls, while survivors in the CT+RT group were significantly older. The proportion of survivors in the CT-only and the CT+RT groups with a lower educational level was significantly higher compared to the control group (4.4% and 19.7% vs 3.3%, respectively, all *P*-values <.01). After adjustment for attained age, survivors in the CT+RT group were significantly less likely to be married or living as married compared to controls and survivors in the CT-only group.

More than one-third of all survivors had been treated with CT as well as RT, 73.4% of whom received cranial RT, while the

TABLE 1 Basic characteristics of subjects in the total ALL survivor group, two treatment subgroups (CT only and CT+RT), and control group

	Survivors			Controls	*P*-value			
	Total (n = 357)	CT only (n = 229)	CT+RT (n = 128)	Total (n = 836)	Survivors vs controls	CT only vs controls	CT+RT vs controls	CT+RT vs CT only
Age at time of study (years), median (IQR)	28.0 (11.1)	25.1 (7.4)	35.2 (8.5)	32.9 (12.4)	<.01	<.01	.04	<.01
≥18.0-24.9	120 (33.6)	112 (48.9)	8 (6.3)	165 (20.0)				
≥25.0-29.9	95 (26.6)	79 (34.5)	16 (12.5)	146 (17.7)				
≥30.0-34.9	62 (17.4)	25 (10.9)	37 (28.9)	177 (21.5)				
≥35.0-39.9	46 (12.9)	7 (3.1)	39 (30.5)	159 (19.3)				
≥40+	34 (9.5)	6 (2.6)	28 (21.9)	178 (21.6)				
Educational level[a]					<.01	<.01	<.01	<.01
Low	35 (9.9)	10 (4.4)	25 (19.7)	27 (3.3)				
Medium	225 (63.4)	153 (67.1)	72 (56.7)	367 (44.3)				
High	95 (26.8)	65 (28.5)	30 (23.6)	434 (52.4)				
Marital status[b]					.01[b]	.52[b]	<.001[b]	.03[b]
Single	103 (28.9)	61 (26.8)	42 (32.8)	148 (17.8)				
Married/living as married	249 (69.9)	165 (72.4)	84 (65.6)	660 (79.3)				
Divorced/widowed	4 (1)	2 (0.9)	2 (1.6)	24 (2.9)				
BMI (kg/m^2), median (IQR)	23.3 (5.7)	22.3 (4.5)	26.0 (7.5)	23.0 (4.9)	.07	.05	<.01	<.01
Ever smoked					<.01	.01	<.01	.10
No	247 (72.0)	154 (69.1)	93 (77.5)	478 (58.7)				
Yes	96 (28.0)	69 (30.9)	27 (22.5)	337 (41.3)				
Age at diagnosis (years), median (IQR)	5.2 (5.9)	5.2 (6.3)	5.1 (5.1)	-		-	-	.90
Time since diagnosis (years), median (IQR)	21.9 (10.4)	18.9 (7.2)	29.3 (6.2)	-		-	-	<.01
Treatment era								<.01
<1984	108 (30.3)	10 (4.4)	98 (76.6)	-		-	-	
≥1984	249 (69.7)	219 (95.6)	30 (23.4)	-		-	-	
Type of CT treatment								
Alkylating agents	184 (52.6)	140 (61.9)	44 (35.5)	-	-	-	-	-
Antimetabolites	349 (99.7)	226 (100)	123 (99.2)	-	-	-	-	-
Mitotic inhibitors	350 (100)	226 (100)	124 (100)	-	-	-	-	-
Antitumor antibiotics	209 (59.7)	143 (63.3)	66 (53.2)	-	-	-	-	-
Platinum-based CT	1 (0.3)	1 (0.4)	0	-	-	-	-	-
Asparaginase	319 (91.1)	222 (98.2)	97 (78.2)	-	-	-	-	-
Type of RT treatment								
Cranial RT only	94 (26.3)	-	94 (73.4)	-	-	-	-	-
Cranial RT + RT other[c]	23 (6.3.)	-	23 (18.0)	-	-	-	-	-
TBI + RT other[d]	11 (3.1)	-	11 (8.6)	-	-	-	-	-
Stem cell transplantation								
Allogeneic	9 (2.5)	1 (0.4)	8 (6.3)	-	-	-	-	-
Autologous	5 (1.4)	-	5 (3.9)	-	-	-	-	-
CED score (mg/m^2)								

(Continues)

TABLE 1 (Continued)

	Survivors			Controls	*P*-value			
	Total (n = 357)	CT only (n = 229)	CT+RT (n = 128)	Total (n = 836)	Survivors vs controls	CT only vs controls	CT+RT vs controls	CT+RT vs CT only
0	166 (47.4)	86 (38.1)	80 (64.5)					
>0 to ≤4000	147 (42.0)	124 (54.9)	23 (18.5)					
>4000 to ≤8000	24 (6.9)	9 (4.0)	15 (12.1)					
>8000	13 (3.7)	7 (3.1)	6 (4.8)					

Note. Values represent numbers (%), unless indicated otherwise. The subcategories may not add up to the total number of women due to missing values.
Abbreviations: CED, cyclophosphamide equivalent dose; CT, chemotherapy; IQR, interquartile range; RT, radiotherapy.
[a]Categorized as low: up to and including lower technical and vocational training; medium: up to and including secondary technical and vocational training; high: up to and including higher technical and vocational training and university.
[b]Corrected for age at time of study.
[c]RT other included: abdominal/pelvic RT (n = 21), spinal RT (n = 19), neck RT (n = 1), or thoracic RT (n = 2).
[d]RT other included: cranial RT (n = 2) or spinal RT (n = 1).

TABLE 2 First pregnancy rates among the subgroup of study participants who are/have been at risk of pregnancy

	Survivors			Controls	OR (95% CI)[a]			
	Total (n = 164)	CT only(n = 86)	CT+RT (n = 78)	Total (n = 455)	Survivors vs controls	CT only vs controls	CT+RT vs controls	CT+RT vs CT only
Ever pregnant								
No (ref.)	25 (15%)	13 (15%)	12 (15%)	38 (8%)	Ref.	Ref.	Ref.	Ref.
Yes	139 (85%)	73 (85%)	66 (85%)	417 (92%)	0.7 (0.4-1.3)	1.2 (0.6-2.6)	**0.4 (0.2-0.9)**	0.4 (0.1-1.2)

Note. Values represent numbers (%), unless indicated otherwise.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Corrected for age at time of study, educational level, and marital status.

remaining 18.0% and 8.6% were treated with cranial RT in combination with other types of RT or TBI (with or without additional RT), respectively (Table 1). Fourteen survivors (3.9% of the total group) received HSCT, of which nine (2.5%) allogeneic and five (1.4%) were autologous. Moreover, eight out of the nine survivors treated with allogeneic HSCT received TBI as part of the conditioning regimen. Of the survivors treated with autologous HSCT, three received TBI.

The CED scores for all survivors are shown in Table 1. The majority of survivors in the CT+RT group had a CED score of 0 (64.5%), while the majority of survivors in the CT-only group had a CED score between >0 and ≤4000 mg/m^2 (54.9%). Three survivors were treated with CT-only conditioning regimens prior to HSCT. All three had a CED score of ≥8000 mg/m^2.

Differences between participating ALL survivors, nonparticipating ALL survivors, and ALL survivors who died after surviving for at least 5 years are shown in Table S1. Differences between clinical and questionnaire-only survivors and controls are shown in Table S2. Compared to questionnaire-only survivors and controls, clinical survivors and controls were similar in terms of attained educational level, BMI, ever having had sexual intercourse, and ever having been pregnant. Clinical survivors were, however, significantly younger compared to survivors completing the questionnaire only, while clinical controls were less likely to be married or living as married.

The timing of the clinical measurement for both clinical survivors and controls is shown in Table S3. For the vast majority of clinical survivors and controls, clinical measurements were performed during the natural cycle.

3.1 | Pregnancy rates

Pregnancy rates among women (ever) at risk for pregnancy were 85% for each of the survivor groups and 92% for the controls (Table 2). Survivors in the CT+RT group appeared to be significantly less likely to have ever been pregnant compared to controls (odds ratio [OR] = 0.4, 95% CI 0.2-0.9), whereas differences in pregnancy rates among the other groups were nonsignificant.

The mean (SD) maternal age at birth of first child for the total survivor group was 27.8 (3.8) years, while this was 26.3 (3.2), 29.1 (3.9), and 29.2 (4.1) years for the CT-only group, the CT+RT group, and the controls, respectively. Corrected for educational level and marital status, only survivors in the CT-only group were significantly younger

TABLE 3 Pregnancy outcomes of first pregnancy among study participants in the total ALL survivor group, two treatment subgroups (CT only and CT+RT), and control group

	Survivors			Controls	OR (95% CI)			
	Total (n = 125)	CT only(n = 67)	CT+RT (n = 58)	Total (n = 391)	Survivors vs controls	CT only vs controls	CT+RT vs controls	CT+RT vs CT only
Pregnancy outcome of first pregnancy[a]								
Live birth								
No	40 (32.0)	27 (40.3)	13 (22.4)	101 (25.8)	Ref.	Ref.	Ref.	Ref.
Yes	85 (68.0)	40 (59.7)	45 (77.6)	290 (74.2)	0.9 (0.5-1.5)[a]	0.8 (0.5-1.6)[a]	1.0 (0.5-2.1)[a]	1.0 (0.4-2.9)[a]
Still birth								
No	125 (100.0)	67 (100.0)	58 (100.0)	388 (99.2)	Ref.	Ref.	Ref.	Ref.
Yes	0	0	0	3 (0.8)	-	-	-	-
Miscarriage								
No	99 (79.2)	52 (77.6)	47 (81.0)	336 (85.9)	Ref.	Ref.	Ref.	Ref.
Yes	26 (20.8)	15 (22.4)	11 (19.0)	55 (14.1)	1.6 (0.9-2.9)[a]	1.8 (0.8-3.8)[a]	1.4 (0.6-3.2)[a]	1.0 (0.3-3.2)[a]
Abortions								
No	111 (88.8)	55 (82.1)	56 (96.6)	348 (89.0)	Ref.	Ref.	Ref.	Ref.
Yes	14 (11.2)	12 (17.9)	2 (3.4)	43 (11.0)	0.9 (0.4-2.0)[a]	1.0 (0.4-2.5)[a]	0.6 (0.1-3.0)[a]	0.4 (0.0-3.1)[a]
Preterm delivery[a,b]								
No	72 (87.8)	36 (92.3)	36 (83.7)	249 (86.2)	Ref.	Ref.	Ref.	Ref.
Yes	10 (12.2)	33 (7.7)	7 (16.3)	40 (13.8)	0.8 (0.4-1.6)[a]	0.5 (0.1-1.7)[a]	1.0 (0.4-2.4)[a]	2.3 (0.5-11.3)[a]

Note. Values represent numbers (%), unless indicated otherwise. The subcategories may not add up to the total number of women due to missing values.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Corrected for age at birth of first child and educational level.
[b]Preterm delivery: delivery before 37 weeks of pregnancy.

at the birth of their first child compared to controls ($P < .01$). Survivors in the CT+RT group were significantly older compared to survivors in the CT-only group at the birth of their first child ($P < .01$) but not compared to controls.

The median (interquartile range [IQR]) time to first pregnancy was 3.0 (6.8), 2.5 (5.0), 3.0 (8.8), and 3.0 (7.0) months for all survivors, survivors in the CT-only group, survivors in the CT+RT group, and controls, respectively. No significant differences in time to first pregnancy were found between any of the (sub)groups.

3.2 | Pregnancy outcomes

No significant differences were found between any of these groups regarding the reported pregnancy outcomes when corrected for age at birth of first child and educational level (Table 3).

3.3 | Other self-reported reproductive characteristics

Mean age (SD) at menarche was 12.9 (1.6), 13.1 (1.6), 12.4 (1.6), and 13.0 (1.4) years for the overall survivor group, the CT-only group, the CT+RT group, and the controls, respectively. Survivors in the CT+RT group were significantly younger at menarche compared to both controls and survivors in the CT-only group (both $P < .01$).

Survivors in the CT+RT group were significantly less likely to ever have had sexual intercourse compared to controls (OR = 0.3, 95% CI 0.1-0.6) (Table 4). Only survivors in the CT+RT group were significantly less likely to ever have had a desire for children, both compared to survivors in the CT-only group (OR = 0.4, 95% CI 0.2-1.0, $P = .049$) and controls (OR = 0.5, 95% CI 0.3-0.9). No significant differences in terms of current or future desire for children were found between any of the (sub)groups.

TABLE 4 Self-reported reproductive characteristics of study participants in the total ALL survivor group, two treatment subgroups (CT only and CT+RT), and control group

	Survivors			Controls	OR (95% CI)[a]			
	Total (n = 357)	CT only (n = 229)	CT+RT (n = 128)	Total (n = 836)	Survivors vs controls	CT only vs controls	CT+RT vs controls	CT+RT vs. CT only
Ever had sexual intercourse[a]								
No	36 (10.3)	20 (8.9)	16 (12.8)	42 (5.1)	Ref.	Ref.	RRef.	Ref.
Yes	313 (89.7)	204 (91.1)	109 (87.2)	787 (94.9)	0.7 (0.4-1.2)	1.2 (0.6-2.2)	**00.3 (0.1-0.6)**	0.3 (0.1-1.0)
Ever had a desire for children[a]								
No/don't know	52 (14.6)	20 (8.8)	32 (25.2)	95 (11.4)	Ref.	Ref.	Ref.	Ref.
Yes	303 (85.4)	208 (91.2)	95 (74.8)	739 (88.6)	0.8 (0.5-1.2)	1.2 (0.7-2.1)	**00.5 (0.3-0.9)**	**0.4 (0.2 - 1.0)**
Current or future desire for children[a]								
No/don't know	120 (35.1)	47 (21.5)	73 (59.3)	352 (43.6)	Ref.	Ref.	Ref.	Ref.
Yes	222 (64.9)	172 (78.5)	50 (40.7)	467 (57.0)	0.8 (0.6-1.2)	0.7 (0.5-1.2)	11.0 (0.6-1.7)	1.1 (0.6 - 2.3)

Note. Values represent numbers (%), unless indicated otherwise. The subcategories may not add up to the total number of women due to missing values.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Corrected for age at time of study, marital status, and educational status.

Eight survivors (2.2%) and one control (0.1%) reported to have entered menopause prematurely (range age at menopause 13-40 years). Seven out of the eight survivors (88%) with a premature menopause had been treated with both CT and RT, of whom four had been treated with HSCT.

For all the self-reported reproductive characteristics (pregnancy rates, pregnancy outcomes, and other self-reported reproductive characteristics), analyses were also performed excluding survivors treated with TBI. For all the previously mentioned results, excluding these survivors did not considerably change the results as described above.

3.4 | Clinical markers of ovarian function

Overall, the proportions of women with low AMH and low AFC values were significantly higher in the total group of survivors compared to controls (Table 5). Survivors in the CT+RT group were significantly more likely to have low AMH, low inhibin B, and low AFC levels compared to controls, and they were also significantly more likely to have low AMH levels compared to survivors in the CT-only group. No significant differences were found between survivors in the CT-only group and controls. However, when survivors treated with TBI (n = 5) were excluded from analyses, only the differences in AFC between survivors in the total survivor group and controls, as well as between survivors in the CT+RT group and controls, remained statistically significant (OR = 4.0, 95% CI 1.2-13.5 and 5.7, 95% CI 1.4-22.6, respectively). After exclusion of all survivors treated with HSCT, statistical significance for differences in AFC between all survivors and controls also disappeared (Table S4). Furthermore, due to low numbers, only OR for the total group versus controls were interpretable after additional exclusion of survivors treated with HSCT.

4 | DISCUSSION

This is the largest and most comprehensive study examining reproductive function in a large nationwide cohort of female childhood ALL survivors by means of both self-reported and clinical outcomes. Our results are reassuring in that survivors treated with CT only were found to have similar pregnancy rates compared to those of controls. Furthermore, they did not differ from controls in terms of other self-reported reproductive outcomes (age at menarche, having had sexual intercourse, desire for children), and did not seem to have decreased ovarian function compared to controls. Lower pregnancy rates were found only among survivors treated with both CT and RT. Additionally, survivors treated with HSCT or TBI were found be at an increased risk of abnormal clinical markers compared to controls.

Our findings regarding pregnancy rates confirm previous reports on ALL survivors, which found pregnancy risk among ALL survivors to be similar to that of controls,[10,12,14] even after adjustment for marital or cohabitation status.[13] Our results also confirm findings from previous studies that show a reduced risk for pregnancy in survivors treated with RT.[9,11,12,14] Cranial RT has been shown to result in an increased risk of experiencing neuropsychological sequelae,[28–31] which could potentially reduce a survivor's chance of finding a partner, thus limiting favorable circumstances for parenthood. Survivors of

TABLE 5 Hormonal and ultrasound characteristics of study participants in the total ALL survivor group, two treatment subgroups (CT only and CT+RT), and control group

	Survivors			Controls	OR (95% CI)			
	Total (n = 183)	CT only (n = 131)	CT+RT (n = 52)	Total (n = 386)	Survivors vs controls[a]	CT only vs controls[a]	CT+RT vs controls[a]	CT+RT vs CT only[a]
Low AMH								
No	163/178 (91.6)	123/128 (96.1)	40/50 (80.0)	362/375 (96.5)	Ref.	Ref.	Ref.	Ref.
Yes	15/178 (8.4)	5/128 (3.9)	10/50 (20.0)	13/375 (3.5)	**2.6 (1.1-5.8)**	1.3 (0.4-4.3)	**7.0 (2.7-18.8)**	**14.5 (3.0-70.7)**
Low inhibin B								
No	155/176 (88.1)	120/126 (95.2)	35/50 (70.0)	327/378 (86.5)	Ref.	Ref.	Ref.	Ref.
Yes	21/176 (11.9)	6/126 (4.8)	15/50 (30.0)	51/378 (13.5)	1.3 (0.7-2.3)	0.6 (0.2-1.5)	**2.2 (1.1-4.6)**	3.6 (0.9-14.2)
Elevated FSH								
No	167/178 (93.8)	124/128 (96.9)	43/50 (86.0)	344/382 (90.1)	Ref.	Ref.	Ref.	Ref.
Yes	11/178 (6.2)	4/128 (3.1)	7/50 (14.0)	38/382 (9.9)	2.3 (0.9-5.4)	3.6 (0.9-14.6)	2.1 (0.8-6.0)	1.9 (0.3-11.6)
Low AFC								
No	145/152 (95.4)	111/113 (98.2)	34/39 (87.2)	327/335 (97.6)	Ref.	Ref.	Ref.	Ref.
Yes	7/152 (4.6)	2/113 (1.8)	5/39 (12.8)	8/335 (2.4)	**4.4 (1.4-14.4)**	1.9 (0.3-11.8)	**7.7 (2.1-28.2)**	5.6 (0.6-52.1)

Note. Values represent numbers (%), unless indicated otherwise. The subcategories may not add up to the total number of women due to missing values. Low AMH and low AFC were defined using age-specific cut-off values (ie, 2 SD below the mean value of the control subjects within the concerning age group). Elevated FSH and low inhibin B were defined using fixed cut-off values (ie, ≥10 U/L and <20 ng/L, respectively).
Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; CI, confidence interval; FSH, follicle-stimulating hormone; OR, odds ratio.
[a]Corrected for age at time of study, hormonal use, and BMI at time of study.

childhood ALL,[15,32,33] and survivors treated with RT in particular,[15,34] have indeed shown to have lower marriage/cohabitation rates compared to reference populations, as confirmed by this study. However, as we controlled for marital status, the reduced pregnancy risks among ALL survivors treated with both CT and RT should be attributed to other factors such as damage to the hypothalamic-pituitary axis (in case of cranial RT) or the ovaries (in case of TBI).

Survivors in the CT-only group were significantly younger at birth of their first child compared to controls. These results are in line with the study of Freycon et al.[14] As CT-only protocols have been implemented in the Netherlands since 1984,[35] the CT-only group in our study comprised the relatively younger survivors. These younger survivors might have received more information regarding possible fertility impairment, as more evidence concerning the late effects of cancer treatment[36,37] has become available over the past decades, and might have been advised not to postpone childbearing for too long.

Additionally, in our study no increased risks of adverse pregnancy outcomes were identified between any of the (sub)groups. Although it seems as if the proportion of live births as a first pregnancy outcome is higher in the combined treatment group compared to the CT-only group, no significant differences between these groups were found after correction for both maternal age at birth of first child and educational level.

Previous studies reported significantly higher rates of miscarriages,[38] abortions,[16] and premature deliveries[39] among survivors of leukemia compared to controls. Only one of these studies included only survivors treated for ALL. This study showed that survivors of ALL treated with craniospinal irradiation are at increased risk of miscarriage, while this was not the case for survivors treated with cranial therapy alone.[16] Since advances in ALL treatment have made the use of spinal irradiation obsolete (and RT in general, in the case of standard risk protocols) in more modern treatment regimens, survivors treated based on contemporary protocols are likely not considered to be at risk for higher miscarriage rates.

Additionally, evidence of luteal phase deficiency (LPD) has been demonstrated in both survivors of childhood cancer who have received ≥22 Gy hypothalamic-pituitary RT [40] and survivors of ALL treated with prophylactic cranial RT.[41] LPD is characterized by inadequate progesterone production during the luteal phase resulting in abnormal endometrial maturation, thereby predisposing to failed or delayed implantation, infertility, and early pregnancy loss.[42] As it is often difficult to distinguish early pregnancy loss, possibly due to LPD, from a late menstrual period, clinically confirmed pregnancies may not necessarily reflect all pregnancies that have occurred in a woman's lifetime. Hence, the pregnancy rates of survivors treated with cranial RT may

be an underestimation of the actual ability to become pregnant. Likewise, the proportion of miscarriages may actually be an underrepresentation of the actual amount of miscarriages that have occurred. Our study confirms earlier findings that ALL survivors treated with RT are at increased risk of an early onset of puberty.[7,43] Additionally, survivors treated with RT were significantly less likely to have ever had sex compared to controls, which is in line with a previous study among leukemia survivors.[44] The fact that excluding survivors treated with TBI did not considerably alter any of the self-reported findings indicates that not only survivors treated with TBI are at risk of adverse reproductive outcomes.

We found that survivors treated with RT have significantly lower AMH, inhibin B, and AFC values compared to controls. Moreover, AMH and AFC levels were reduced among the total group of ALL survivors. Excluding survivors treated with TBI from this analysis showed that only differences in AFC remained significant for both the total group and survivors treated with RT. However, after the exclusion of survivors treated with any kind of HSCT, statistically significant differences in AFC disappeared for the total group of survivors and controls, while results for the other participant groups and markers became uninterpretable.

This suggests that differences in AMH, inhibin B, and AFC levels were mostly due to TBI treatment, which is known to significantly reduce ovarian function,[45,46] or due to the conditioning regimen that includes high doses of alkylating agents. As only three survivors were treated with HSCT without having received TBI, numbers were too low to conduct analyses on this group.

Recently, Krawczuk-Rybak et al evaluated ovarian reserve in adolescent and young adult survivors of childhood ALL treated according to high-, intermediate-, and low-risk treatment protocols.[17] AMH levels were found to be significantly lower only among survivors in the high-risk group compared to controls (mean ± SD were 2.56 ± 2.15 and 4.13 ± 3.19 ng/mL, respectively, $P = .003$). Similarly, they also found no significant differences regarding levels of FSH, inhibin B, and AMH between survivors that were and were not treated with RT.

Furthermore, the attained age of the clinical study participants could have been too low for differences in FSH values between survivors and controls to become apparent, as in our study the clinical survivors and controls differed significantly in terms of attained age (median attained age 26.2 and 32.4 years, respectively).

In our study, (subgroups of) survivors did not differ from controls in terms of AFC. Morphological studies of ovaries have shown that AFC values are reduced in children with leukemia.[47,48] However, Bath et al[49] demonstrated that AFC was not reduced in a group of female cancer survivors, most of which had been diagnosed with ALL, compared to controls. Based on our results, treatment for ALL (in the absence of TBI or HSCT) does not seem to cause a reduction in ovarian reserve.

Strengths of this study include the large size of the eligible cohort of female childhood cancer survivors as well as the large number of study participants. Moreover, the fact that our study included both self-reported data and data on several clinical markers among a group of survivors of childhood ALL specifically is a unique asset compared to other studies investigating reproductive function among childhood cancer survivors.

However, there are also some limitations. First, clinical participants were significantly younger compared to questionnaire-only participants, suggesting our study has been subject to some degree of bias. This may be due to the fact that survivors completing the questionnaire only may have already achieved their reproductive goals or that they are no longer pursuing these. As such, they may be less interested in having their reproductive function assessed clinically, as opposed to younger survivors who are yet to start a family or have not yet completed their wish to have (multiple) children. This may have limited the generalizability of study results and could possibly have resulted in an over- or underestimation of the prevalence of an impaired ovarian function or ovarian reserve. Second, the self-reported outcomes may have been subject to recall bias. Furthermore, the number of women who reported certain adverse pregnancy outcomes (ie, abortions and preterm deliveries) is rather small, slightly compromising interpretations of the results. Finally, our results on menopausal status should be interpreted with caution, since our study population consisted of relatively young women due to a limited follow-up time. Therefore, not all women who will develop a premature menopause may have been identified yet. Extended follow-up data are necessary in order to determine whether ALL survivors indeed are at increased risk of a premature menopause.

In conclusion, ALL survivors treated with CT only do not differ from controls regarding timing of menarche, virginity status, their desire for children, pregnancy rates, or adverse pregnancy outcomes. However, ALL survivors treated with a combination of CT and RT seem to be at increased risk of several adverse reproductive outcomes. Female childhood ALL patients, especially those survivors having been treated with RT, need to be informed about the potential late effects on fertility. Survivors not treated with TBI or HSCT are not at risk of a diminished reproductive function. Those that were treated with TBI or HSCT can be advised not to delay childbearing, and should be referred to fertility specialist if desired.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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