

Fertility in Women Treated With Cranial Radiotherapy for Childhood Acute Lymphoblastic Leukemia[†]

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Background. Fertility impairments among women treated during childhood for cancer are known to occur after some, but not all, types of anticancer therapy. Although leukemia is the most common cancer of childhood, until now fertility in survivors has not been comprehensively assessed. **Procedure.** We investigated functional impairment of fertility in women who were long-term survivors of acute lymphoblastic leukemia (ALL) with a retrospective cohort study. Proven fertility (defined as ever pregnant) was evaluated by self-report among 182 females treated on protocols of the Children's Cancer Group (age at interview, 22.6 years on average) and 170 controls drawn from among the survivors' female siblings (23.4 years). The interview included psychosocial inventories designed to detect mood problems. **Results.** Significant

fertility deficits were noted in female survivors treated with cranial radiotherapy (CRT) at any dose around the time of menarche (relative fertility (RF)) = 0.27, 95% CI = 0.09, 0.82, $P = 0.03$). Controlling for marital status, mood at interview, and many fertility-related situations did not change the association. **Conclusion.** This study provides evidence for fertility deficits after treatment for ALL with CRT, and, in addition, for the first time, suggests that girls treated around the time of menarche are especially at risk. Clinical confirmation of these results is needed. If gonadal damage occurs in women receiving these treatments, their risk for further sequelae, such as osteoporosis and heart disease, may be significantly raised, requiring active management and intervention. *Pediatr Blood Cancer* 2004; 42:589–597. © 2004 Wiley-Liss, Inc.

Key words: childhood cancer; fertility; leukemia; menarche; radiotherapy

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood and, in the United States, occurs at a rate of 3.4 cases per 100,000 children aged 0–14. In 1996, ALL constituted 24.1% of all newly diagnosed cancers. As the continuing success of modern cancer treatment has pushed 5-year relative survival after leukemia diagnosis beyond 70% for some groups [1], long-term complications of therapy, including fertility, take on greater significance for survivors and their families.

Treatment-related fertility deficits are known to occur based on data from retrospective cohort studies of survivors of the most common types of childhood cancer [2,3], but leukemia survivors were not represented in large numbers in these studies. The only study so far to evaluate proven fertility after childhood leukemia [4] showed a significant drop in female fertility following chemotherapy and cranial radiation.

Studies that evaluated structural damage to the ovaries, gonadotropin levels, and alterations in the timing of menarche all provide evidence in support of the hypothesis that fertility impairments may follow treatment of girls for childhood leukemia [5–12]. Since the potential for recovery of reproductive function is impressive in both males and females [13], the long-term consequences of these clinical changes remain to be established.

In order to evaluate proven fertility in survivors of childhood ALL, the National Institutes of Health collaborated with the Children's Cancer Group (CCG L891), a

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national collaborative oncology group, to construct a large cohort of male and female ALL survivors diagnosed during childhood and adolescence and sibling controls. This report concerns the fertility of female survivors.

MATERIALS AND METHODS

Eligibility Requirements

A list of all children newly diagnosed with ALL between 1970 and 1987 and treated on clinical trials was provided by the Children's Cancer Group (now subsumed into the Children's Oncology Group, COG). Patients treated for ALL on protocols 101, 105, 106, 123, 139, 141, 141A, 162, 162A, 163, 903, 9998 were included. To be eligible for this study, each survivor had to be at least age 18, in continuous remission (without further treatment), and to have survived at least 2 years since diagnosis. The eligibility requirements for controls specified that only one control per family was chosen. Controls had to be at least 18 years of age within the 9 months following the survivor's interview. If more than one sibling was eligible, the person closest in blood relationship, sex, and date of birth, in that order, was selected. Telephonic interviews (conducted between 1990 and 1991) were carried out with the survivors and controls only; no proxies were interviewed. The proportion of survivors who could not be located was 9.3%, and the refusal rate was 7.2%. The corresponding proportions for controls were 8.8% and 7.5%. Details of institutional and individual participation were previously published [14].

For this analysis of fertility, further eligibility criteria were applied. The analytic approach considered time (years) to first pregnancy for all subjects (survivors and controls) who ever had sexual intercourse, considering the first pregnancy as an event. Person-years were counted from age 18 or 2 years from diagnosis (for survivors) whichever was later. We excluded subjects whose first pregnancy occurred before cohort entry, and subjects with unknown age of first pregnancy. The eligibility requirements for the study overall meant that, to be old enough to be in the reproductive years, the average age of survivors was older than expected from an incidence series. This difference also meant that survivors who were younger at diagnosis were more likely to be younger at interview, resulting in considerable confounding between age at diagnosis and relative fertility (RF).

Data Collection

Telephonic interviews dealt with basic demographic information, education of parents and respondent, dates and duration of special schooling, marital status, including live-in relationships, their number and duration, history of sexual intercourse, including age at first sexual intercourse, number of sexual partners and frequency of

intercourse in the past month. A series of questions was asked about female health conditions, including endometriosis, pelvic inflammatory disease, venereal disease, fibroids, polycystic ovaries and galactorrhea, as well as hysterectomy, tubal ligation, and oophorectomy. The section on menstrual history covered age at first menses, currently menstruating spontaneously, spontaneous onset of menses and reasons for never menstruating, age and treatment for each condition, regularity of and problems with menstruation, including duration and treatment. In order to determine attitudes towards pregnancy, we asked a series of questions about family plans, including doctors' advice about having children and fertility tests, intentions about having children, attitudes towards the health of children, history of trying to become pregnant and frequency of intercourse, history of clinical infertility ("did you ever have sexual intercourse for 1 year or more without using contraception and not become pregnant?"), ever seek medical assistance with fertility issues, reasons, any diagnosis and any treatment for infertility. Other questions covered pregnancy history, health, and risk-taking behavior. Contraceptive history and months of unprotected intercourse was not sought due to time constraints. Instead the questions mentioned above explicitly dealt with intentions and attitudes towards pregnancy and problems with fertility.

Proven fertility was defined as ever having had a pregnancy, including miscarriage, stillbirth, or ectopic pregnancy. Since pregnancy can be a matter of choice as well as biology, respondents also completed a measure of affective state or mood, the Profile of Mood States (POMS). This is a 65-item self-report questionnaire designed to measure six mood states (tension/anxiety, depression, anger, confusion, vigor, and fatigue) with demonstrated reliability and validity. POMS has been used successfully with cancer patients [15,16]. Use of POMS total score to summarize the strong correlations between the subscales has proved to be a valid and useful way to report on the findings [17]. Data concerning treatment with radiotherapy and chemotherapy, relapse, and bone marrow transplant (BMT) was abstracted from the survivors' clinical records maintained by the Children's Cancer Group.

Statistical Analysis

The study design was a retrospective cohort with siblings as the control cohort. Pregnancy event rates were calculated as the number of events divided by the person-years contributed by each subject. In order to control for age differences between survivors and controls and potential confounding arising from age at diagnosis and follow-up, age since cohort entry was divided into two intervals, 18–21 and 22+ years. Thus, women could have contributed person-years to the first interval and, if they

had not become pregnant, also contributed person-years to the second interval, depending on their age at interview. This allowed age-specific pregnancy rates to be calculated for each age interval, although pregnancy rates in the open-ended second interval may be higher for controls than survivors, since they contributed more person-years. Doses of cranial radiotherapy (CRT) specified by CCG clinical trials were none, 18 or 24 Gy. However, clinical records indicated that some individuals received slightly different doses. For this reason, CRT was categorized as none, 1–18 Gy, or more than 18 Gy, which was mostly 24 Gy. Among survivors, 22.8% received alkylating agents and 82.6% received intrathecal methotrexate.

Standard methods for analysis of continuous (*t*-test) and categorical (chi-square) data were used to compare characteristics of survivors and controls. The relative risk (RF) was used to define the difference between survivors and controls and was calculated as the age-specific pregnancy rate among survivors divided by the same rate among controls. Heterogeneity between strata was tested by the Breslow–Day method. Associated hypothesis tests and confidence intervals (CIs) were obtained under the assumption that the rates were constant over each age interval and that the observed number of events followed a Poisson distribution [18,19]. Since puberty marks a watershed in susceptibility to fertility damage following cancer treatment, and previous analyses had linked altered menarcheal timing with treatment [11], survivors were divided into three groups based on the difference between age at diagnosis and (self-reported) age at menarche. The three groups consisted of those diagnosed at ages younger than 2 years before menarche, a middle group of survivors diagnosed around the time of menarche, that is, 2 years before or after menarche, and the older group of survivors diagnosed more than 2 years after menarche. Although the proportional hazards model was the preferred way to evaluate the effects of potentially confounding variables [20], when the proportional hazards assumption was evaluated by testing whether the relative risks varied with time for subgroups defined by age at treatment in relation to age at menarche, it was found to violate the assumption. However, the model was used to evaluate the influence of marriage as a time-dependent covariate on survivor/control RF. In general, we used the age-specific person-years approach with stratification to evaluate the influence of other factors on the observed effects. Mantel–Haenszel chi-squares were used to calculate summary odds ratios. Calculations were carried out with SAS (SAS Institute, Inc., Cary, NC).

RESULTS

From the original 291 female survivors and 220 female controls included in this study, those eligible for this cohort analysis comprised 182 female survivors and 170

TABLE I. Characteristics of Female Leukemia Survivors and Female Sibling Controls

	Survivors (N = 182)		Sibling controls (N = 170)		P
	N	%	N	%	
Age at leukemia diagnosis (year)					
<4	13	7.1	—	—	
5–9	72	39.6			
10–14	64	35.2			
15–17	33	18.1			
Year of diagnosis					
1970–74	53	29.1	—	—	
1975–79	74	40.7			
1980–84	44	24.2			
1985–86	11	6.0			
Age at interview (year)					
18–19	36	19.8	11	6.5	
20–24	90	49.5	69	40.6	
25–29	48	26.4	54	31.8	
30–34	8	4.4	24	14.1	
35–41	0	0	12	7.1	<0.0001
Age at first menses (year)					
9–11	30	16.7	26	15.4	
12–13	96	53.3	95	56.2	
14–15	36	20.0	35	20.7	
16–19	18	10.0	13	7.7	0.86
Ever married, or had a live-in relationship					
Yes	88	48.4	109	64.1	0.003
Age at first marriage (year)					
18–19	29	34.1	28	26.9	
20–24	46	54.1	57	54.8	
25–29	10	11.8	19	18.3	0.35
Ever pregnant					
Yes	57	31.3	79	46.5	0.004
Age at first pregnancy (years)					
18–19	19	32.8	26	32.9	
20–24	32	55.2	39	49.4	
25–29	7	12.1	11	13.9	
30–31	0	0	3	3.8	0.47

female controls. Table I lists their characteristics. Age at diagnosis was skewed towards older ages since this is a survival series, with entry into the cohort at age 18. Thus, average age at diagnosis was 10.7 years. The largest group of survivors (40.2%) was diagnosed and treated during the late 1970s. Survivors were younger than controls at interview (*P* < 0.0001), with an average age for survivors of 22.6 compared to controls, 23.4 years old. Survivors were less likely than controls to have married (*P* = 0.003), although the distribution of age at first marriage was similar in the two groups. The proportion ever pregnant was smaller for survivors than controls (*P* = 0.004). The number of patients who were enrolled on each CCG protocol follows the protocol number in parenthesis: 101 (50), 105 (12), 106 (7), 123 (1), 139 (3), 141 (33), 141A (13), 162 (36), 162A (12), 163 (6), 903 (7), 9998 (2).

Unadjusted pregnancy rates (Table I) indicate that survivors are much less likely than controls (31.3% for survivors compared to 46.5% for controls, *P* = 0.004) to

become pregnant. However, the presence of potential confounding is indicated by differences between the two groups in both age at interview and in marriage rates (48.4% for survivors compared to 64.1% for controls, $P=0.003$). Tables II and III use a stratified analysis approach to evaluate the ways in which selected characteristics affect the differences between the two groups in unadjusted pregnancy rates. Table II sets out summary fertility relative risks within levels of age at diagnosis, and year of diagnosis, age at interview and age at first menses, educational level and average high school grades, smoking, marital status, and age at first marriage. In all cases, the fertility deficit among survivors is maintained, as indicated by the summary relative risks and CIs. Table III sets out fertility-related variables in a similar manner in order to evaluate the ways in which fertility practices influenced fertility for both survivors and controls. None of these variables, including frequency of sexual intercourse in the recent past, consult the doctor about trouble getting pregnant, having intercourse with the intention of getting pregnant and frequency of intercourse during those times as well as the clinical definition of infertility—ever have intercourse for more than 1 year

without using contraception and not get pregnant—change the fertility deficit, with one exception. That is, all survivors and controls that had intercourse more frequently than once weekly while trying to get pregnant succeeded. However, the numbers are small, and do not change the summary fertility relative risk. The Breslow–Day test is not statistically significant for any category, suggesting that there is no significant heterogeneity between strata on any variable.

In other stratified analyses (not shown), we compared fertility odds ratios for levels of learning disability, special education, ever in a gifted or talented program, currently menstruating, menstruated in the last 6 months, or menstrual disturbances for which subjects sought medical advice, by drug use, part-time employment, religion, occupation, or self-reported health status. Other fertility-related questions (ever have a hysterectomy or oophorectomy, take fertility drugs, intend to adopt children, or number of sexual partners) do not influence the fertility deficit among survivors. Moreover, no statistically significant differences are present in mood disturbances (either total score or any of the subscales) between survivors who were pregnant and those who were never pregnant

TABLE II. Effect of Selected Characteristics on Relative Risk of Fertility in Leukemia Survivors and Sibling Controls

Characteristic	Survivors		Controls		MH fertility relative risk	95% CI	B–D test for homogeneity
	N	%	N	%			
Age at diagnosis							
0–11	23/93	24.7	—	—			
12+	34/89	38.2			0.65	0.42, 1.01	—
Year of diagnosis							
1970–76	33/88	37.5	—	—			
1977–86	24/94	25.5			0.84	0.69, 1.03	—
Age at interview							
18–20	5/61	8.2	3/23	13.0			
21–24	16/65	24.6	17/57	29.8			
25+	36/56	64.3	59/90	65.6	0.91	0.70, 1.18	0.8
Age at first menses							
9–12	24/76	31.6	36/73	49.3			
13–18	32/104	30.8	43/96	44.8	0.72	0.57, 0.91	0.8
Educational level							
High school or less	31/79	39.2	38/61	62.3			
More than high school	26/103	25.2	41/109	37.6	0.70	0.55, 0.88	0.4
Average grade in high school							
A	9/36	25.0	10/37	27.0			
B or less	48/146	32.9	66/129	51.2	0.73	0.58, 0.91	0.3
Smoking level							
Never smoked	37/132	28.0	44/107	41.1			
Ever smoked	20/50	40.0	35/63	55.7	0.74	0.59, 0.93	0.9
Ever married							
Yes	45/88	51.1	70/109	64.2			
No	12/94	12.8	9/61	14.8	0.81	0.63, 1.03	0.5
Age at first marriage							
<20	9/18	50.0	12/17	70.6			
20+	34/65	52.3	53/87	60.9	0.78	0.57, 1.08	0.5

MH, Mantel–Haenszel test; B–D, Breslow–Day test.

TABLE III. Effect of Fertility-Related Issues on Relative Risk of Fertility in Leukemia Survivors and Sibling Controls

Characteristic	Survivors		Controls		MH fertility relative risk	95% CI	B-D test for homogeneity
	N	%	N	%			
Frequency of sexual intercourse in past month							
Never	10/47	21.3	11/36	30.6			
1-2 times	11/40	27.5	12/22	54.6			
More than two times	33/85	38.8	52/105	49.5	0.75	0.59, 0.95	0.5
Ever see a doctor about trouble getting pregnant?							
Yes	31/61	50.8	9/16	56.3			
No	26/121	21.4	70/154	45.5	0.65	0.52, 0.83	0.2
Did you ever have intercourse with the intention of starting a pregnancy?							
Yes	25/32	78.1	51/55	92.7			
No	32/149	21.5	28/115	24.4	0.85	0.67, 1.08	0.1
Frequency of intercourse when trying to get pregnant							
Once weekly	14/20	70.0	32/35	91.4			
More than once weekly	11/11	100.0	19/19	100.0	0.46	0.24, 0.86	—
Ever have intercourse for more than 1 year and not become pregnant?							
Yes	9/11	81.8	19/19	100.0			
No	16/20	80.0	32/35	91.4	0.49	0.28, 0.86	0.3

MH, Mantel-Haenszel test; B-D, Breslow-Day test.

(total POMS scores 28.9 vs. 21.9, respectively), or when stratified by dose of CRT (total POMS scores for high CRT, 21.4 vs. 19.0), or on a number of other parameters.

Time to First Pregnancy Analysis

Previous studies had indicated that major effects on fertility would be due to the type of treatment received and/or the age at which survivors were treated. Of the 182 survivors, 27 had pregnancies during the ages 18-21, and another 30 had pregnancies at ages over 21. The corresponding numbers for the 170 controls were 43 and 36, respectively. Overall, fertility of female survivors is significantly less (RR = 0.60) than that of controls during the ages 18-21, (P = 0.04; Table IV). At older ages, first pregnancy rates are similar between survivors and controls (RF = 1.18, NS).

When the effects of different treatments are considered (Table IV), there is no suggestion that spinal radiotherapy or alkylating agent chemotherapy contribute significantly to the overall fertility deficit. The fertility deficit present at younger follow-up ages (18-21) was seen in children diagnosed at ages 0-9 (RR = 0.72), and later (RR = 0.51), but only reached statistical significance (P = 0.04) for children diagnosed after age 9. However, fertility of survivors who received CRT at any dose is only half that of controls for pregnancies during ages 18-21. When both CRT levels are combined, survivors have a significant impairment in fertility (RF = 0.53, P = 0.02) at ages 18-21. There is no dose-response effect seen in these data; fertility rates are approximately equal for both CRT doses. There are significantly fewer than expected first pregnancies at younger ages among women treated (ever) with

intrathecal methotrexate (ITMTX) (RF = 0.54, P = 0.02). However, most (91%) of women treated with CRT also received ITMTX; doses of ITMTX are similar for women who had ever been pregnant versus those who had not (103 g vs. 96 g, respectively). The apparent fertility deficit associated with ITMTX can, thus, be explained by CRT.

After age 21, fertility of survivors is slightly higher than that of controls, though not significantly so, for each stratum of each factor. There is no suggestion that RF is depressed. Subsequent analyses are restricted to women who were treated with CRT (Table V). Taking the three diagnosis-to-menarche time periods into account, there is a relative dearth of pregnancies to survivors during the ages 18-21 when treated before or during menarche with CRT. The RF is 0.55 for women treated before menarche, and barely escapes being statistically significant; RF is even lower for treatment around menarche (RF = 0.27, 95% CI = 0.09, 0.82) and is clearly statistically significant. After age 21, RF is not different for survivors treated before or during menarche, but is higher than controls when treated after menarche (RF = 1.93, 95% CI = 1.02, 3.70, P = 0.04). The lower panel of Table V shows the same comparison for married women only. For married women, the main effects seen above are unchanged, though the smaller numbers of subjects widens the CIs. Thus, for married women, treatment during menarche carries a RF of 0.35 during ages 18-21, while for married women treated after menarche, RF during ages 22 and older is 1.94. We further evaluated the role of pregnancy in a proportional hazards model with marriage as a time-dependent covariate, restricted to women treated with CRT less than 2 years after menarche. In a model with two terms, one for survivor/control status and one for

TABLE IV. Age-Specific First Pregnancy Rates of Sexually Active Female Leukemia Survivors and Female Sibling Controls According to Survivors' Treatment, per 1,000 Person-Years

	First pregnancies occurring between 18 and 21 years of age					First pregnancies occurring after age 21				
	No. of Events	No. of PY	Rate ×1,000	RR [¶]	P*	No. of events	No. of PY	Rate ×1,000	RR [¶]	P*
Sibling controls	43	432.6	99.4			36	351.6	102.4		
Survivors, overall	27	449.2	60.0	0.60	0.04	30	247.1	121.2	1.18	0.5
Survivors by treatment										
Cranial radiotherapy by dose										
None	5	36.6	136.6	1.37	0.5	2	11.1	180.5	1.76	0.4
1–18 Gy	10	190.9	52.4	0.53	0.07	12	92.5	129.8	1.27	0.5
>18 Gy	12	221.7	54.1	0.54	0.06	16	143.6	111.4	1.09	0.8
Radiotherapy by site										
No spinal RT	20	359.7	55.6	0.56	0.03	25	190.4	131.3	1.28	0.3
Spinal RT	7	89.5	78.2	0.79	0.5	5	56.7	88.2	0.86	0.8
Alkylating agent chemotherapy										
With alkylators	4	97.6	41.0	0.41	0.09	7	35.4	192.2	1.88	0.13
No alkylators	23	351.6	65.4	0.66	0.11	23	210.7	109.2	1.07	0.8
Intrathecal methotrexate										
Ever	20	370.6	54.0	0.54	0.02	24	192.7	124.6	1.22	0.5
Never	7	78.6	89.2	0.90	0.8	6	54.5	110.2	1.08	0.9
Age at diagnosis										
0–9	14	194.6	72.0	0.72	0.3	7	47.0	149.0	1.46	0.2
10+	13	254.6	51.1	0.51	0.04	23	200.2	114.9	1.12	0.7

CRT, cranial radiotherapy; RT, radiotherapy.

*Compares age-specific pregnancy rates for survivors in each category with pregnancy rates for sibling controls, unadjusted for marital status.

¶Relative Risk

marriage, RF of survivors was 0.65 (95% CI = 0.42, 0.99, *P* = 0.0497). Thus, we may conclude that marriage deficits do not account for the observed fertility deficit.

The Kaplan–Meier survival curves show that perimenarcheal treatment with any dose of CRT is associated with depressed fertility, without any suggestion of recovery for as far as they have been followed-up (Fig. 1). The

fertility deficit for survivors treated around menarche is statistically significant in a proportional hazards analysis (*P* = 0.037). Fertility of survivors in the two groups treated before and after menarche suggests an initial decrement in fertility for both groups, followed by an acceleration for women treated after menarche (Fig. 2). However, these differences do not reach statistical significance.

TABLE V. Age- and Marriage-Specific Fertility Relative Risks (RR) in Relation to Age at Menarche and According to Survivors' Age at Diagnosis

Group	Age 18–21				Age 22+			
	N	RR	95% CI	P	N	RR	95% CI	P
Married and unmarried subjects								
Sibling controls	43				36			
Survivors by interval between diagnosis and menarche								
More than 2 years before	12	0.55	0.30, 1.02	0.07	8	1.00	0.46, 2.20	1.00
Within 2 years	3	0.27	0.09, 0.82	0.03	7	0.70	0.31, 1.57	0.40
More than 2 years after	6	0.76	0.33, 1.79	0.53	13	1.93	1.02, 3.70	0.04
Married subjects only								
Sibling controls	31				29			
Survivors by interval between diagnosis and menarche								
More than 2 years before	7	0.72	0.32, 1.63	0.4	6	1.09	0.46, 2.60	0.80
Within 2 years	3	0.35	0.11, 1.14	0.08	5	0.63	0.25, 1.62	0.30
More than 2 years after	5	0.76	0.30, 1.95	0.6	12	1.94	1.00, 3.74	0.05

Relative risks compare unadjusted first pregnancy rates (per 1,000 person-years) for leukemia survivors with sibling controls.

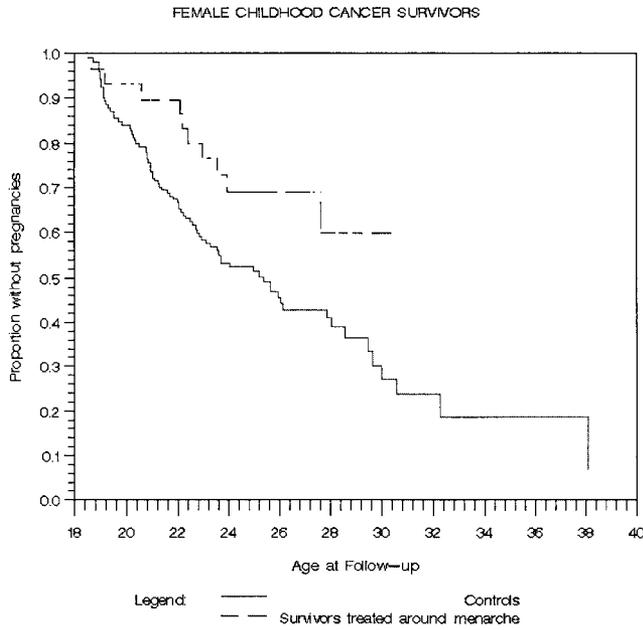


Fig. 1. Kaplan–Meier survival curves of time to first pregnancy for female sibling controls (solid line) and female survivors treated around the time of menarche with any dose of cranial radiotherapy ($P = 0.037$).

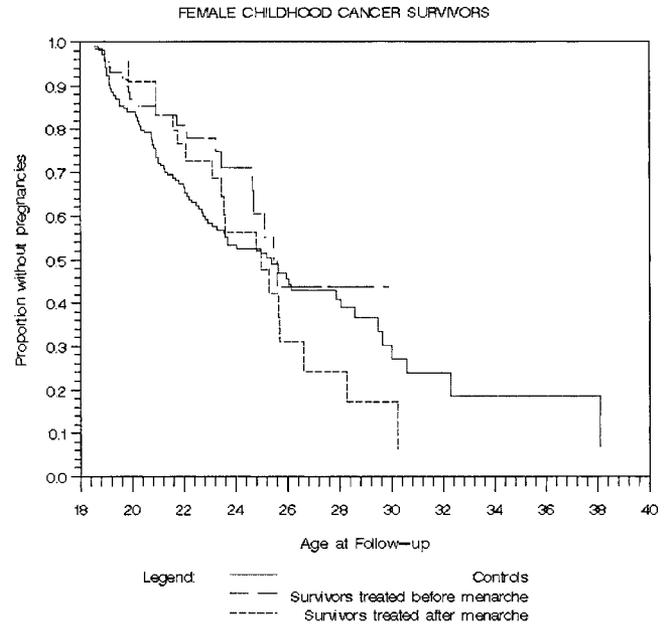


Fig. 2. Kaplan–Meier survival curves of time to first pregnancy for female childhood leukemia sibling controls (solid line) and survivors treated with any dose of cranial radiotherapy before and after menarche. These differences do not reach statistical significance.

DISCUSSION

In this study, the fertility rate of women treated for ALL during childhood with any dose of CRT was significantly lower than that of sibling controls. Further, the timing of CRT may be crucial: treatment within 2 years of menarche, either before or after, conferred an added risk, reducing fertility between the ages of 18 and 21 to only about one-quarter that of controls (RF=0.27). Further, we speculate that fertility patterns for those survivors who were treated after menarche suggested that they may have postponed pregnancy until they were older, since, following an initial lag, fertility rates accelerated (Table V; Fig. 2).

There are number of choices and life-style situations that could bear on these findings. Previous analyses of other endpoints in these data have revealed significant deficits in school performance [14] and alterations in the (self-reported) timing of menarche [11]. Zeltzer et al. [17] reported significant mood disturbances among female survivors in this cohort and Glover et al. [21], related significant distress among survivors at follow-up to high-dose CRT among other life-style factors. These results suggest possible intervening pathways to impaired fertility. For instance, impaired intellectual functioning could result in survivors having a poorer self-image, which could make them less likely to be marriage partners; alterations in timing of menarche could be related to disturbances in fertility; and, being older, controls have more chance to marry and have children. These and other

pathways meant that the potential impact of these factors had to be evaluated before we could claim a fertility deficit. When we assessed RF in relation to all of these factors, and a number of others related to life style and fertility choices, the fertility deficit was unchanged. We used age-specific rates to control for the age differences between survivors and controls, and analyzed the data with and without unmarried subjects; in both cases, survivors' fertility deficit persisted. In addition, it is unlikely that psychosocial issues explain this result, since mood differences were not associated with fertility deficits.

These results may have other explanations arising from treatment. For instance, either radiation to the region of the ovaries or high-dose alkylating agent chemotherapy can cause primary gonadal failure [9,22] even in young girls [10]. However, in our study neither spinal nor abdominal radiotherapy, nor treatment with alkylating agent chemotherapy was associated with a statistically significant fertility deficit. The fertility deficit cannot be explained by treatment with BMT, since no survivors eligible for this analysis were treated with BMT.

Previous studies of proven fertility are limited in their ability to shed light on our observation. However, in the NCI-sponsored Five Center Study, women treated for all childhood cancers combined showed some evidence for fertility depression following treatment with radiotherapy above the diaphragm (relative risk = 0.78, CI: 0.63–0.96) [3], but leukemia survivors could not be studied separately due to small numbers. Our results are consistent with the only study to evaluate female fertility following childhood

leukemia that showed that fertility of women treated with chemotherapy and cranial radiation together was significantly reduced (RR = 0.39) compared to women treated with chemotherapy only [4]. There is some clinical support for these observations: Bath et al. [23] assessed adult hypothalamic-pituitary-ovarian function after ALL, and found subtle ovulatory disorders that they related to CRT. However, proven fertility was not evaluated in that study.

Most unexpected is the association of fertility impairments with treatment around the time of menarche. Although CRT has been associated with early onset of puberty [11], there are no previous reports linking CRT treatment around the time of menarche with any evidence of impaired hypothalamic-pituitary function. Reports of damage to other endocrine systems may support our observation. For instance, some studies report greater endocrine impairment among children if CRT was administered early in childhood [24] and obesity is more likely in children diagnosed before age 7 [25].

Clinically apparent gonadotropin deficiency has been recorded primarily in children receiving more than 30–40 Gy radiation to the hypothalamus/pituitary for solid tumors [26]. Our study suggests that irradiation of the hypothalamic-pituitary area with doses in the range of 18–24 Gy, when administered to females around the time of menarche, may result in subtle abnormalities that may affect fertility. It is possible that radiation-induced changes to the hypothalamus might interfere with the normal gonadotropin releasing hormone “pulse-generator.” This could interfere with the normal pulsatile release of luteinizing hormone/follicle stimulating hormone (LH/FSH) and perhaps impair the mid-cycle LH peak that is a prerequisite for normal ovulation.

Endocrine damage is known to occur after CRT in these dose ranges. In this same group of ALL survivors, Mills et al. [11] reported two separate effects of treatment on the timing of menarche. ALL survivors who received 18 Gy cranial radiation before the age of 8 years had significantly earlier menarche and survivors who received 24 Gy of craniospinal radiation at any age had significantly later menarche than controls. Growth hormone deficiency, drop in final height and obesity, possibly mediated via central nervous system damage, have been reported in survivors of ALL [22,27–29].

We set out to evaluate the potential effect on fertility of psychosocial disturbances resulting from treatment. In the absence of a prospective study, we measured mood at the time of interview, many years after therapy. Although mood disturbance was not associated with treatment or fertility in this study, it is possible that other psychological disturbances could impact fertility. For instance, we speculate that survivors treated well before and well after menarche may have voluntarily postponed their fertility. Additional focussed questioning and careful

clinical evaluation may shed light on these issues of choice and biology.

This cohort of female survivors of childhood leukemia was treated on some of the earliest large-scale clinical trials for ALL in the US with treatments that are no longer in general use. Our results are not intended to apply to newly diagnosed patients today, but to the estimated 6,000 adult female survivors in the United States, and more in the United Kingdom and elsewhere who may have received these therapies. Use of prophylactic CRT has been largely replaced by intrathecal chemotherapy and is now used only for carefully selected patients. Fertility impairment in this cohort of women treated during childhood for ALL affected fully half of the cohort. Future studies of endocrine levels linked to functional fertility may reveal mechanisms of damage. If infertility is confirmed in this group of ALL survivors, the consequences of early menopause, such as osteoporosis and cardiovascular disease, are substantial and require careful follow-up.

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