Reproduction Following Treatment for Childhood Leukemia: A Population-Based Prospective Cohort Study of Fertility and Offspring

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Of all children diagnosed with leukemia in Denmark, Finland, Iceland, Norway, and Sweden, 981 had discontinued therapy before 1985 and had been followed up annually after cessation of therapy. Progeny was registered and fertility evaluated among survivors who passed age 18 years without a relapse (n = 299).

By April 1989, 48 offspring were registered, one of whom had congenital anomalies. This was no more than expected from the incidence of birth defects in the general population. No childhood malignancies or genetic diseases have so far been diagnosed in the progeny. In the study group, none of the 19 female and 8 male survivors of myeloid leukemias had become parents, and only 4 fathers were reported among the 131 male survivors of acute lymphoblastic leukemia (ALL). However, 23 of the 149 females treated for ALL had delivered 41 children.

Fertility was measured as cumulative rates of first birth by maternal age. In a Cox regression analysis, cases who had received prophylactic radiation of the central nervous system (CNS) had a lower first birth rate than those without radiation (rate ratio 0.39, 95% CI 0.15-1.00), indicating that doses of 18-24 Gy to the brain may possibly be a risk factor.

By using the Norwegian birth cohort of 1966 as a control group, matching the median year of birth for the study subjects, the group of female ALL survivors as a whole was as likely as the general female population to have given birth up to the age of 23.

The first generation of females successfully treated for childhood ALL seems to have a nearly normal reproductive pattern during young adulthood, without increased risk of congenital anomalies in the offspring. However, cranial radiation as CNS prophylaxis may possibly impair subsequent reproduction.

Key words: leukemia in childhood, long-term survivors, antineoplastic agents adverse effects, radiotherapy adverse effects, fertility, birth defects

INTRODUCTION

The prospect of potential cure for childhood leukemia induced concern about late adverse effects of the disease and its treatment, and it was recognized that impaired fertility in the survivors as well as genetic disease in the offspring could possibly be expected [1-4]. Long-term follow-up studies of large patient cohorts were needed to evaluate the clinical importance of these late effects and relate them to specific diseases and therapy.

The 5 Nordic countries have a total of 23 million inhabitants. Well-organized national health systems enable identification of selected patient populations. This prompted a prospective follow-up investigation of all childhood leukemia patients who had discontinued treatment [5-9]. The objectives of the present study were to compare fertility in the patient group with that of the normal population, and to identify predictive factors.

Neuroleukemia prophylaxis had been given as radiotherapy (RT) to 58% of all ALL patients in the cohort, enabling us to study radiation as one factor possibly influencing subsequent fertility. We also wished to...
investigate occurrence and nature of anomalies and malignancies in the offspring of survivors of childhood leukemias.

MATERIALS AND METHODS

Patients

Of all children diagnosed before age 15 with childhood leukemias, 981 had elected to discontinue therapy by 1985; 963 in primary and 18 in a later remission. By April 1989, 763 patients from the complete cohort had survived without relapse. The patients ranged in age from 18 to 42 years, but only 30 cases had a period ranging from 4.3 to 26.5 years.

In the study group, 280 cases were survivors of ALL; 149 females and 131 males with median birth year 1966 and 1967, respectively. At last follow-up, the females ranged in age from 18 to 42 years, but only 30 cases had passed age 25. With a few exceptions of long-term survivors after bone marrow transplantation (BMT), the ALL patients had been treated according to various contemporary chemotherapy (CT) protocols [10–14]. Prophylaxis against CNS leukemia was gradually introduced during the years 1971–1973. Methotrexate (MTX) intrathecally, later combined with systemic infusions, was the method of choice in Norway and Iceland [10]. Intrathecal MTX combined with cranial radiation (RT) 18–24 Gy was the standard procedure elsewhere. Of the adult female ALL patients without RT, 33 cases had not received any CNS prophylaxis, 35 had been given MTX, and 78 had also received RT.

Methods

Patients were included in the study from 1962 until 1985, and annual information was collected directly from physicians in all departments treating and controlling the patients [9]. They provided, on a patient by patient basis and from the year of cessation of therapy, data on relapses, deliveries, life status, and time last seen. Last data collection was completed April 1, 1989. Medical status in the offspring was also reaffirmed at that point.

Fertility in the 149 female adult survivors of ALL was measured as birth rate by maternal age at first delivery, calculated according to the Kaplan–Meier method [15]. Censoring was mainly at the age achieved when the study closed, but in addition, cases were censored at relapse (n = 5), death (n = 3), and when lost to follow-up (n = 9). Fertility estimates for different treatment groups were compared using the logrank rest [16], with a significance level at 5%. The Cox regression model [17] was used to estimate fertility rate ratios comparing patients with and without radiation, while simultaneously controlling for the effects of the following covariates: age at diagnosis (3 categories), age at cessation of therapy (3 categories), and calendar year of treatment start (4 categories). The fertility rate ratios, as measure of relative risk, were reported with 95% confidence intervals (CI).

The Norwegian female birth cohort of 1966 with 31,186 individuals was chosen as a reference, permitting comparison until age 23. The population at risk was defined as the midyear population according to data from the Norwegian Central Bureau of Statistics. The Norwegian Medical Birth Registry provided annual parity- and age-specific birth numbers, enabling calculation of cumulative birth rates according to the life table method [15,18,19,21].

The MEDLOG biomedical computer program was used for calculations.

RESULTS

Among the 299 adult survivors of childhood leukemias, 27 patients treated for ALL had become parents (Table II). No children were born to or sired by survivors of myeloid leukemias.

Twenty-three of the 149 adult female ALL survivors had delivered 41 children. Most of the mothers had been on antileukemic therapy at least partly during puberty: Seventeen were above 10 years of age and 8 were 15 years or older at cessation. Treatment had been completed prior to conception in all but one patient who conceived while still on maintenance therapy with 6-mercaptopurine (6-MP) (case 1). Medication was withheld in

<table>
<thead>
<tr>
<th>Table I. Adult Survivors of Childhood Leukemia (160 Females, 159 Males) by Diagnosis and Main Treatment Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>ALL (n = 280)</td>
</tr>
<tr>
<td>Females</td>
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<tr>
<td>Males</td>
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<tr>
<td>AML (n = 17)</td>
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<tr>
<td>Females</td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td>CML (n = 2)</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Total no. of cases</td>
</tr>
</tbody>
</table>

*ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CML, chronic myeloid leukemia; CT, chemotherapy; RT, radiotherapy.
### TABLE II. Survivors With Progeny After Cessation of Therapy for ALL*

<table>
<thead>
<tr>
<th>Sex &amp; case no.</th>
<th>Year of birth</th>
<th>Age at diagnosis</th>
<th>Treatment length</th>
<th>Years after cessation</th>
<th>Age</th>
<th>Offspring (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>1947</td>
<td>12</td>
<td>7</td>
<td>0</td>
<td>19</td>
<td>3</td>
<td>6-MP in first trimester</td>
</tr>
<tr>
<td>2</td>
<td>1949</td>
<td>13</td>
<td>2½</td>
<td>11½</td>
<td>27</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1953</td>
<td>4½</td>
<td>15</td>
<td>2½</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1954</td>
<td>14</td>
<td>7</td>
<td>2½</td>
<td>23½</td>
<td>2</td>
<td>Relapse during initial therapy</td>
</tr>
<tr>
<td>5</td>
<td>1956</td>
<td>7½</td>
<td>10</td>
<td>1</td>
<td>18½</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1958</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>25½</td>
<td>1</td>
<td>Cyclo; relapse in fourth pregnancy</td>
</tr>
<tr>
<td>7</td>
<td>1959</td>
<td>3½</td>
<td>5½</td>
<td>15½</td>
<td>24½</td>
<td>2</td>
<td>Relapse during initial therapy</td>
</tr>
<tr>
<td>8</td>
<td>1960</td>
<td>8</td>
<td>7</td>
<td>11½</td>
<td>26</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1961</td>
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<td>5</td>
<td>12½</td>
<td>21</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1961</td>
<td>11½</td>
<td>3</td>
<td>6</td>
<td>20½</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1961</td>
<td>3½</td>
<td>8½</td>
<td>12</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1962</td>
<td>5½</td>
<td>6</td>
<td>7</td>
<td>18½</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1962</td>
<td>9½</td>
<td>4½</td>
<td>1</td>
<td>15</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1963</td>
<td>8</td>
<td>5</td>
<td>7½</td>
<td>20½</td>
<td>2</td>
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</tr>
<tr>
<td>15</td>
<td>1963</td>
<td>7½</td>
<td>5</td>
<td>11</td>
<td>23½</td>
<td>2</td>
<td></td>
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<tr>
<td>16</td>
<td>1965</td>
<td>3½</td>
<td>5½</td>
<td>11</td>
<td>20</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1965</td>
<td>4½</td>
<td>5</td>
<td>9½</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1965</td>
<td>13½</td>
<td>2½</td>
<td>2½</td>
<td>18½</td>
<td>2</td>
<td>MTX</td>
</tr>
<tr>
<td>19</td>
<td>1966</td>
<td>10</td>
<td>4</td>
<td>7</td>
<td>21</td>
<td>1</td>
<td>RT; Cyclo; CNS-tumour, mors</td>
</tr>
<tr>
<td>20</td>
<td>1967</td>
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<td>3</td>
<td>7½</td>
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<td>MTX</td>
</tr>
<tr>
<td>22</td>
<td>1968</td>
<td>4½</td>
<td>3</td>
<td>13</td>
<td>20½</td>
<td>1</td>
<td>RT</td>
</tr>
<tr>
<td>23</td>
<td>1969</td>
<td>6½</td>
<td>2</td>
<td>11½</td>
<td>20</td>
<td>1</td>
<td>MTX</td>
</tr>
</tbody>
</table>

\[ n = 23 \]

| Males         |               |                  |                  |                       |     |               |          |
|---------------|---------------|------------------|------------------|                       |     |               |          |
| 24            | 1956          | 4                | 2                | 19½                   | 25½ | 2             |                      |
| 25            | 1958          | 10               | 6½               | 9                     | 25½ | 3             | Cyclo; first children twins |
| 26            | 1965          | 9½               | 3                | 10½                   | 23  | 1             | RT                  |
| 27            | 1967          | 13               | 3½               | 4½                    | 21  | 1             | RT                  |

\[ n = 4 \]

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*Time intervals in years. CNS, central nervous system; Cyclo, cyclophosphamide; M, median; MTX, methotrexate (intravenous + intrathecal); RT, radiotherapy (CNS-prophylaxis); 6-MP, 6-mercaptopurine.

The antileukemic treatment in 4 of the early patients had only included 6-MP and prednisone. The remaining mothers had been treated with combinations of at least prednisone, vincristine, 6-MP, and MTX. Two cases had been given maintenance therapy with cyclophosphamide. Thirteen of the mothers had been treated before the introduction of CNS prophylaxis. Of the remaining cases, 4 had received intrathecal MTX and MTX infusions (0.5 g/m²). 5 had received cranial and one craniospinal radiation. All patients had remained in remission after cessation of therapy when their first child was born. One patient suffered a relapse during a later pregnancy (case 7), and another developed a brain tumour and died a year after having delivered her first child (case 19).

Of the 131 adult male survivors of ALL, four had fathered 7 children. None of the fathers had had testicular involvement of the disease or had been given testicular RT. Two of the patients had been older than 15 years of age at cessation of therapy, which in one of them included maintenance with cyclophosphamide.

### Cumulative First Birth Rates by Maternal Age

The life table estimate of fertility until age 23 for the patient group as a whole was not significantly lower than that of the controls, 21.1% compared to 29.5% (Fig. 1). Full follow-up times also beyond that age were...
Fig. 1. Cumulative rates of first birth by age in females previously treated for childhood acute lymphoblastic leukemia (cases, \( n = 149 \)) compared to the Norwegian birth year cohort of 1966 (controls, \( n = 31,186 \)).

Included in the Kaplan–Meier analysis of the patients (Fig. 2). The group as a whole had a fertility rate of 32.3% at 25 years, and it was lower in patients with radiotherapy than in those without \((P = 0.043)\). Excluding cases with bone marrow transplantation, 78 cases of whom 6 were mothers had received CNS-RT, resulting in an estimate of 18.4% at age 25. The corresponding estimate was 41.0% for the 68 cases treated exclusively with CT, 17 of whom had delivered. The unadjusted fertility rate ratio for patients with RT compared to those without was 0.39 (95% CI 0.15–1.00). It was not materially altered after adjustment for calendar year at treatment start, age at diagnosis, and age at ended therapy. Limiting the comparison to patients treated in the era of CNS prophylaxis, patients given combined systemic and intrathecal MTX had a higher fertility rate than those who were irradiated, but the difference was not statistically significant (data not shown).

**Offspring**

All but one of the 48 live born children were without malformations. The first of two children born to case 11 had multiple congenital defects and died 13 months old. The mother was 24 years old at delivery 12 years after cessation of therapy. The infant was small for gestational age, had exophthalmus, low-sitting ears, marked neck fold, abnormalities of the toes, and profound generalized hypotonic musculature. Internal abnormalities included left-sided pelvioureteric stenosis with hydronephrosis and agenesis of the right kidney. Chromosome analysis was normal.

The remaining children ranged in age from several weeks to 23 years, and had been observed for a total of 284 person years when the study ended. None of them was diagnosed with childhood cancer or genetic disease. First daughter born to patient case 1 had 3 healthy children of her own.

**DISCUSSION**

Reproduction depends on a complex of biological and psychosocial factors, and cancer survivors may differ from their peers in many ways that can influence subsequent parenthood. Some patients tend to confirm their ability for pregnancy at an early age [22], others delay family life, are less likely to marry, or decide not to have children [2,23,24]. Leukemia per se does not seem to result in limited reproductive capacity, except after gonadal involvement. However, in addition to the psychosocial long-term effects of life-threatening disease during childhood and adolescence, fertility may be impaired by exposure to chemotherapy, radiotherapy, and surgery.

The main drugs associated with the achievement of long-term disease-free survival in ALL have been combinations of prednisone, vincristine, L-asparaginase, 6-mercaptopurine, and methotrexate, and later also cy-
phamide may cause cessation of germ cell production, and cytosine arabinoside has also been incriminated [3,36-39]. This effect may to some extent be dose related and has been observed in males treated before as well as during and after puberty [3,38,40-43]. The concept that the prepubertal testis may be less susceptible remains to be proven in humans; some studies suggest a higher risk in the sexually more mature patients [33], others show no age relationship [35,39,42]. Although return of spermatogenesis may occur even after a prolonged period of time [3,34,41], a fertility deficit after alkylating agents has been shown in long-term survivors [33].

Radiotherapy may also impair gonadal function [44]. Endocrine abnormalities resulting from cranial radiation including the hypotalamic–pituitary axis may result in deficiencies of anterior pituitary hormones most commonly in the order of growth hormone, gonadotrophins, corticotrophins, and thyrotrophin. Detrimental effects on the CNS tend to be delayed, and it has been shown in a recent study of adult patients that the number and severity of deficiencies increase with time after radiation [45]. Craniospinal radiation, resulting in scatter doses to the gonads, may also cause primary ovarian dysfunction, as shown in a study where ALL patients with this type of CNS prophylaxis were compared to a group with only cranial radiation [48]. Doses of 400 cGy to the ovaries may result in permanent sterility in young females [44,47,48], and doses of 140-300 cGy may cause permanent aspermia in males [33,42,44]. Reduced testicular size and impaired sperm production have been associated both with cranial and testicular radiation [49].

Generational genetic damage from preconceptional exposure of germ cells to radiotherapy or chemotherapy could result in increased incidence of miscarriages and spontaneous abortions, as well as birth defects, malignancies, and genetic disease in the offspring. Clinical studies with this in mind have been conducted since the early 70’s [1], but have not proven any increased incidence of disease in the offspring due to anticancer treatment. Although most reports are limited to anecdotal case series, some larger studies supporr this contention [30,50,51]. The apparent lack of affected offspring may possibly be because lethal cell events caused by drugs or radiation prevent the induced abnormalities from being transferred to the next generation. Offspring of atomic bomb victims exposed to single dose radiation did not have a significantly increased incidence of congenital abnormalities or malignancies [52,53]. However, the possibility of generational genetic damage via viable germ cells is supported by a report of increased incidence of childhood leukemia and lymphoma among children fathered by workers exposed to high doses of radioactive in a nuclear plant before conception [54], as well as the report of induced chromosomal aberrations present in functional human sperm years after therapeutic ionizing radiation [55].

![Fig. 2. Cumulative rates of first birth by age in females previously treated for childhood acute lymphoblastic leukemia, according to treatment category.](image-url)
Our study supports the contention that antileukemic chemotherapy alone does not adversely effect reproduction in young females who were treated for ALL during childhood. However, although the birth rate in the complete group of such subjects was not significantly lower than in the general population, cases with CNS-RT were less likely to have given birth than those without. If the difference observed between these two treatment groups reflects an adverse effect due to radiotherapy, the pathogenesis remains to be identified. Spinal radiation was not a routine part of CNS prophylaxis in any of the Nordic protocols, so ovarian damage is unlikely. While it was not a routine part of CNS prophylaxis in any of the groups reflects an adverse effect due to radiotherapy, the complete group of such subjects was not significantly lower than in the general population, resulting in births. Many individuals start sexual and family life before formal arrangements, and we also found the risk for pregnancy practically difficult to quantify. Some fertility analyses are restricted to married individuals not known to be sterile or voluntarily infertile [33]. However, patients as well as controls were included in the analyses regardless of marital/cohabitation status. In population-based studies, fertility implies de facto reproduction, measured in rates of live births or as proportion with achieved parenthood [20,21], and we evaluated fertility according to this interpretation.

The birth cohort of 1966, matching the median year of birth for the study cases, was used as control group in spite of the disadvantage of short observation time. Although the period total fertility rate in Norway has been virtually constant since 1977, median age at first birth, defined as the age at which half of the individuals in a cohort have at least one child, has increased by more than 2 years since the 1951 birth cohort. It is now expected to have risen beyond age 25 [20], and this trend is similar in all the Nordic countries.

The leukemia survivors are a diverse group in terms of diagnostic subclassification, therapy exposure, age parameters, and hence also with regard to potential late adverse effects. The overall fertility estimate may conceal considerable variability. Our analyses did not reveal any influence of age at diagnosis or age at ended therapy. In this context it may be noted that the majority of mothers had been treated during puberty, an age at which the reproductive system is thought to possibly be more vulnerable to damage than in earlier childhood. The multiplicity of drug combinations, doses, and treatment durations thwarted attempts to separate other factors in a meaningful manner for analysis. Nearly one-third of the adult females had been treated before the era of CNS prophylaxis and according to early systemic treatment principles. Although highly insufficient by modern standards and often of much longer duration, these treatment modalities could possibly have caused less late adverse effects than intensive chemotherapy does. Calendar year of diagnosis, indirectly reflecting intensified treatment protocols, was not significantly associated with reduced fertility. However, our results must be interpreted with care for prediction of fertility and future offspring in patients treated with newer regimens; longer and larger follow-up studies are needed to prove any possible differences.

In addition to obtaining higher precision, a repeat study in 10 years could show if the fertility deficit in
patients with RT compared to those without remains significant when the analysis is restricted to modern treatment groups, where all patients have received intensive chemotherapy and CNS prophylaxis. Also, with a first birth rate estimate closer to a lifetime probability of parenthood, the effects of some of the social factors mainly influencing reproductive differences in early adulthood would be diminished, and the potential effects of late neuroendocrine damage and early menopause would have time to become evident.

In conclusion, our results indicate that chemotherapy alone, in doses and combinations given to the first generation of ALL survivors, does not result in reduced female fertility in young adulthood. However, radiation as CNS-prophylaxis may possibly be a risk factor, even without the spinal component. This study also suggests that the therapy schedules used do not adversely affect the next generation with regard to congenital anomalies.

ACKNOWLEDGMENTS

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