FERTILITY AND PREGNANCY OUTCOME AFTER ABDOMINAL IRRADIATION THAT INCLUDED OR EXCLUDED THE PELVIS IN CHILDHOOD TUMOR SURVIVORS

HÉLENE SUDOUR, M.D.,* PASCAL CHASTAGNER, PH.D.,* LINE CLAUDE, M.D.,†
EMMANUEL DESANDES, M.D.,‡ MARC KLEIN, PH.D.,§ CHRISTIAN CARRIE, M.D.,‡
AND VALERIE BERNIER, M.D.‰

Departments of *Paediatric Onco-Hematology and †Endocrinology, CHU Nancy, Vandoeuvre-lès-Nancy, France; ‡Department of Radiotherapy, Centre Léon Bérard, Lyon, France; §Department of Statistics, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France; and ‰Department of Radiotherapy, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France

Purpose: To evaluate fertility after abdominal and/or pelvic irradiation in long-term female survivors.

Methods and Materials: Puberty and pregnancy outcome were analyzed in female survivors of childhood cancer (aged <18 years) treated with abdominal and/or pelvic radiotherapy (RT) at one of two French centers (Nancy and Lyon) between 1975 and 2004. Data were obtained from medical records and questionnaires sent to the women.

Results: A total of 84 patients who had received abdominal and/or pelvic RT during childhood and were alive and aged more than 18 years at the time of the study made up the study population. Of the 57 female survivors treated with abdominal RT that excluded the pelvis, 52 (91%) progressed normally through puberty and 23 (40%) had at least one recorded pregnancy. Of the 27 patients treated with pelvic RT, only 10 (37%) progressed normally through puberty and 5 (19%) had at least one recorded pregnancy. Twenty-two women (seventeen of whom were treated with pelvic RT) had certain subfertility. A total of 50 births occurred in 28 women, with one baby dying at birth; one miscarriage also occurred. There was a high prevalence of prematurity and low birth weight but not of congenital malformations.

Conclusions: Fertility can be preserved in patients who undergo abdominal RT that excludes the pelvis, taking into account the other treatments (e.g., chemotherapy with alkylating agents) are taken into account. When RT includes the pelvis, fertility is frequently impaired and women can have difficulty conceiving. Nevertheless, pregnancies can occur in some of these women. The most important factor that endangers a successful pregnancy after RT is the total dose received by the ovaries and uterus. This radiation dose has to be systematically recorded to improve our ability to follow up patients. © 2010 Elsevier Inc.

Abdominal and pelvic irradiation, Female, Puberty, Fertility, Births.

INTRODUCTION

Major advances in the treatment of childhood cancer have resulted in markedly improved cure rates over the last two decades, with 5-year overall survival rates of about 75%. It has been estimated that, by the year 2010, about 0.2% of the adult population will have been treated for cancer during childhood (1). This has led, however, to increasing concerns about reduced quality of life in later years in these patients stemming from the late adverse effects of treatment (chemotherapy, radiotherapy [RT], and surgery). These adverse effects include growth disorders; endocrine, cardiac, pulmonary, and renal dysfunction; and neurocognitive deficits, as well as subfertility and infertility, which can have a severe psychosocial impact.

Several treatment modalities have been linked to subfertility and infertility in adulthood in female patients, particularly abdominal RT and total body irradiation that expose the ovaries and/or the uterus to radiation. However, the exact extent of the problems with subfertility and infertility in this population of patients has not been thoroughly investigated in recent years. This study was therefore undertaken to evaluate the effect of abdominal RT that excluded or included the pelvis on puberty, fertility, and pregnancy outcome in female survivors of childhood cancer.

METHODS AND MATERIALS

In a search of patient records at two French institutions (University Hospital, Nancy, and Centre Léon Bérard, Lyon), we identified...
96 previously untreated women who had been treated with RT for cancer between January 1975 and December 2004. All were aged less than 18 years when they were treated and had survived to greater than 18 years of age. All were treated with abdominal RT that excluded or included the pelvis, and none underwent a bilateral ovariectomy, hysterectomy, or cranial irradiation at the time of RT. Of the 96 patients, however, 12 were lost to follow-up, which left 84 patients for our analysis.

Study records
The medical records of the patients were examined to obtain the following information: age at the time of treatment, histopathologic diagnosis, and treatment characteristics. All patients were treated according to national protocols that included multiagent chemotherapy. However, we only analyzed the use of alkylating agents as a potential risk factor. In terms of RT, field borders, doses, and the fractionation scheme were recorded. The border between the abdomen and pelvis was defined as the L5/S1 interspace.

After we obtained the approval of the Information and National Liberty Committee, a questionnaire was sent to the 84 female patients. The first questions asked about puberty, and the others asked about any pregnancies and their outcome (e.g., miscarriages, births, gestational age, and birth weight).

Estimation of delivered radiation doses
At the time these patients were treated with RT, the dose received by the reproductive organs was not systematically recorded. Therefore we had to estimate this dose using the following method: First, we assumed that the two ovaries in the pelvis were opposite S2 to S3 and that the upper limit of the superior aspect of the uterus was opposite S3 to S4. Therefore, if the irradiation field included the pelvis, the mean dose received by these organs was estimated by determining their theoretic places on the dosimetry schemes (Figs. 1 and 2). If the fields did not include the pelvis, we estimated the mean dose received by the uterus and ovaries (by scatter near the field) based on a mathematic model generated by the physicians of the cancer center, as shown in Fig. 3.

Statistical methods
Fertility was defined as the “biological ability to conceive.” On the basis of this definition, we separated the women into three groups:

- The fertile (F1) group of women was considered to have a definite ability to conceive because they had had at least one recorded pregnancy.
- The potentially fertile (F2) group consisted of women who had progressed normally through puberty with spontaneous, regular menstruation and so were probably able to conceive but as yet had no recorded pregnancy.
- The difficult fertility (F3) group consisted of women who had had no spontaneous menstruation and no recorded pregnancies; from this, we surmised that they were not able to conceive and were infertile.

Medical records were compared among the three groups to identify potential risk factors for infertility (e.g., age at the time of treatment, tumor type, irradiation fields, and chemotherapy with alkylating agents). We used the chi-square test for the analysis of qualitative factors and the analysis of variance test to analyze quantitative factors. The F1 and F2 groups were compared with the F3 group by use of the latter test. A logistic regression test with the odds ratio (OR) set at exact 95% confidence intervals (CIs) was used to evaluate the statistical significance of fertility according to the different risk factors found in the univariate analysis.

The major pregnancy outcomes (miscarriage, stillbirth, live birth, term birth, and birth weight) were determined and compared with the observations in the general population.

All statistical analyses were done by use of SPSS software, version 9.0 for Windows (SPSS, Chicago, IL) (2).

RESULTS
Of the 84 patients, 57 were treated in Nancy and 27 in Lyon. In our analysis no distinction was made regarding the treatment center. Of the girls, 50 (59.5%) were treated before the onset of puberty and 34 were treated after the onset of puberty. The median age at the time of RT was 11.3 years (range, 10 months to 17.6 years). Tumor types consisted of nephroblastomas \( n = 29 \), germ cell tumors \( n = 8 \), bone or soft-tissue sarcomas \( n = 13 \), neuroblastomas \( n = 3 \), and Hodgkin lymphoma \( n = 31 \).

The pelvis was included in 27 patients (32.2%): the target volume was the entire abdomen in 6 girls, the hemipelvis in 7, the sacroiliac region in 5, the lumbaoartic and lumbosacral region in 5, and the iliac region in 4. In these 27 girls, all reproductive organs were in the radiation field. However, the ovaries were protected in 8 girls by ovarian transposition, and the uterus was protected in 6 girls by a lead shield. The median dose delivered to the treatment field was 40 Gy (range, 15–64 Gy); the median dose delivered to the ovaries was 6 Gy (range, 0 Gy [in patients who had undergone ovarian transposition] to 60 Gy); and the median dose delivered to the uterus was 20 Gy (range, 1 Gy [in patients protected with lead shielding] to 54 Gy).

The radiation field excluded the pelvis in 57 patients (67.8%). The median dose delivered in these patients was
27 Gy (range, 15–64 Gy), with the reproductive organs receiving only scattered radiation. We estimated that the median dose delivered to the ovaries and uterus was 1 Gy (range, 0–7 Gy) and 1 Gy (range, 0–4 Gy), respectively.

All patients were treated by national multiagent chemotherapy protocols; 50 (59.5%) of these patients were treated with alkylating agents. The mean cumulative dose of cyclophosphamide was 3.3 g/m² (range, 2–6 g/m²), and the mean cumulative dose of ifosfamide was 29.8 g/m² (range, 7.5–54 g/m²).

At the time of the study, the median time that had elapsed since the end of treatment was 18.1 years (range, 1.2–38.6 years), and the median age of the women was 27.1 years (range, 18–45 years). Of the 84 women, 70 (83%) returned their questionnaires. The information about puberty and menstruation was known for all 84 women from their medical records. Of the 14 patients who did not return a questionnaire, we assigned those who progressed normally through puberty to the F2 group and those who did not progress normally through puberty to the F3 group.

**Fertility of study cohort**

The 28 women (33.3%) in the F1 (fertile) group had at least one recorded pregnancy. Of these women, 12 had had 1 baby, 12 had had 2 babies, 2 had had 3 babies, and 2 had had 4 babies. One baby died just after birth, for a total of 49 living babies in the 28 women. Thus the fertility index in this group was 1.8 children per woman. Seventeen pregnancies resulted in miscarriage.

The 34 women (40.5%) in the F2 (potentially fertile) group had spontaneous, normal menstruation but no recorded pregnancies: 25 have not tried to become pregnant and 9 did not return the questionnaire, but these latter women have not had any children to the best of our knowledge.

The 22 women (26.2%) in the F3 (difficult fertility) group did not have spontaneous menstruation and had no recorded pregnancies (3 have tried unsuccessfully to become pregnant). Five of these women did not answer the questionnaire.

In the univariate analysis we did not observe patient age at the time of treatment, the time of treatment in relation to puberty, or the tumor type to have any significant influence on fertility. Several treatment characteristics did, however, show a significant impact on fertility. These were direct pelvic irradiation, the total irradiation dose, the radiation dose delivered to the reproductive organs, and treatment with alkylating agents.

- With regard to direct pelvic irradiation, among the 28 women with at least one baby, the pelvis has been irradiated only in 5 cases (18%).
- The total irradiation dose appeared to be significantly higher in the F3 group than in the F1 and F2 groups ($p = 0.05$).
The dose delivered to the reproductive organs appeared to be the most important risk factor. The dose delivered to the ovarian cortex (both ovaries) was as follows: 2.1 ± 1.4 Gy and 3.8 ± 7.2 Gy in the F1 group, 3.5 ± 7.2 and 2.2 ± 2.6 Gy in the F2 group, and 14.9 ± 16.2 Gy (same dose for both ovaries) in the F3 group (p < 0.005). The dose delivered to the uterus was 4.9 ± 9.8 Gy in the F1 group, 3.5 ± 6.9 Gy in the F2 group, and 18.2 ± 14.6 Gy in the F3 group (p < 0.0005). Of the 3 women treated after the onset of puberty, among the 28 women who achieved pregnancy, the maximal dose estimated to have been delivered to the ovarian cortex was 8 Gy and the maximal dose estimated to have been delivered to the uterus was 25 to 30 Gy.

Treatment with alkylating agents was also found to have had a significant negative impact on fertility (p = 0.04). However, we attributed this result to a poor synergistic effect of the alkylating agents with RT, since the chemotherapy doses per se in 95% of the women were below the threshold known to cause infertility.

In the multivariate analysis direct pelvic irradiation (OR, 17.6; 95% CI, 5.2–59), the dose received by the ovaries and uterus (OR, 1.1; 95% CI, 1.05–1.19), and the combination of RT and alkylating agents (OR, 4.2; 95% CI, 1.3–14) were all found to be significant risk factors for subfertility (Tables 1 and 2). Specifically, abdominal irradiation that included the pelvis and the use of alkylating agents were responsible for a 17.7 and 4.2 relative risk of subfertility, respectively. Moreover, 5-Gy and 10-Gy increases in the dose received by the reproductive organs multiplied the risk of infertility by 1.6 and 2.6, respectively. When the data are examined in terms of a risk threshold, it becomes clear that even very low radiation doses (i.e., 3–4 Gy to the ovaries or uterus) can cause problems with fertility in adulthood. That is, the delivery of radiation doses to these organs of only below 4 Gy appears to be free of the risk of problems with fertility, depending also on the associated treatment. This cohort was too small to show whether there was any variation in this threshold according to the age of the patient.

### Efficacy of techniques to preserve fertility

Two techniques were used to protect the ovaries from radiation exposure in the girls who underwent pelvic irradiation. The first was ovarian transposition, in which, generally, the ovaries were moved to a paracolic position. This was performed in 8 of the girls. Six went on to have spontaneous menstruation, and three had a successful pregnancy. These 3 patients had hormonal treatment to induce regular menstruation, however. The second technique was lead shielding of the uterus, which was used in 6 patients. Of these 6 women, 3 had a successful pregnancy.

### Delivery and pregnancy outcomes

Six women delivered via caesarean section. During surgery, one obstetrician noted 1 woman to have a particularly thin and fibrotic uterus with a very atrophic myometrial muscle, suggesting a high risk of rupture.

Among the 57 women who received abdominal RT that excluded the pelvis, there were 53 pregnancies leading to 36 live births and 17 miscarriages. Among the 27 women who had abdominal RT that included the pelvis, there were 14 pregnancies leading to 10 live births and 4 miscarriages.

Among the 28 women who had had at least 1 successful pregnancy, the babies were born prematurely in 8 women (this occurred in the first pregnancy in 6 women). Of the 49 offspring, 11 (22%) were born prematurely between 33 and 37 weeks’ gestation. Only 1 was born before 32 weeks’ gestation. The birth weight was less than 2,500 g in 7 babies (14%) born of 6 women. However, we failed to find a relationship between birth weight and the radiation dose received by the uterus. One baby was born with a clubfoot. At the time of the study, all of these children were healthy and meeting normal developmental milestones (Table 2).

### DISCUSSION

Because of the retrospective nature of this study, there are several clear limitations. The first is that the radiation doses delivered to the reproductive organs were determined...
a posteriori by interpretation of the dosimetry results, and the doses of the alkylating agents received and their real influence were also determined retrospectively. A second limitation of our study is the small size of the cohort, which did not allow us to prove the influence of many relevant factors such as age. A third and final limitation is that the interval from the time of treatment to the time of the analysis was not long enough in many patients. This would potentially make for a large number of patients being designated as potentially fertile who are actually fertile. For that reason, we considered the two together in our analysis of threshold doses. Despite these limitations, we were still able to make some interesting conclusions. It is also important to note that reports of pregnancies and live births in childhood cancer survivors who receive abdominal irradiation are rare (3–5). Thus our study helps fill an important void in the literature.

Prior studies that have focused on these same issues have suggested a pronounced radiosensitivity of the ovarian cortex (6–8). In the same vein, we found that the most important risk factor for subfertility was the radiation dose received by the ovaries and the uterus. Specifically, only doses below 4 Gy appear not to be associated with subfertility. This is in accordance with the findings of Wallace et al. (6), who found the LD50 (i.e., the dose required to kill 50% of the total oocytes) to be 2 Gy or less.

It has been shown that the degree of impairment of fertility depends on the patient’s age at the time of treatment. This has to do with the fact that the younger the patient is at the time of RT, the greater is the size of her oocyte pool. Thus, for a given dose of radiation, the proportionate reduction in the size of this pool is of greater relevance than the degree of ovarian damage per se (7, 8). In this regard, Brougham and Wallace (8) have shown that the sterilizing dose (i.e., the dose at which premature ovarian failure occurs immediately after treatment in at least 95% patients) declines with the age of the patient at the time of treatment, with a sterilizing dose of approximately 15 Gy for women aged less than 20 years.

We failed, however, to find an influence of age at the time of RT because the size of our cohort was small. Nonetheless, for the cohort as a whole, we found that only doses of less than 4 Gy caused no damage. From this finding, it is apparent that doses of between 4 and 15 Gy put patients at risk of subfertility that depends on their age and associated treatment.

It has often been noted that the reduction in the oocyte pool is the factor most responsible for reducing the window of reproductive potential (9, 10). Indeed, as Larsen et al. (9) noted, the presence of menstruation at the end of treatment does not necessarily connote normal fertility because it is the window that is, in fact, narrowed. In our study the lack of long-term follow-up from the time of RT did not allow us to draw conclusions in this regard.

It is well recorded that the type of chemotherapy, especially the use of alkylating agents, can also accelerate ovarian degeneration (10). We likewise found that chemotherapy with alkylating agents created an additional risk of subfertility. The total dose and the age of the patient at the time of treatment (i.e., the older the patient, the more severe the damage) are additional factors (10).

In female patients abdominal RT that includes the pelvis may also affect uterine function. In this regard, we found that the dose received by the uterus had a significant impact.

### Table 2. Combined results

<table>
<thead>
<tr>
<th>Menstruation</th>
<th>Abdominal RT alone (n = 57)</th>
<th>RT including pelvis (n = 27)</th>
<th>No. of pregnancies</th>
<th>No. of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>54 (95%)</td>
<td>11 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hormonal treatment</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td>At least 1 recorded</td>
<td>23</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No attempt</td>
<td>25</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attempt and failure</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertile group (n = 28)</td>
<td>23 (40%)</td>
<td>5 (19%)</td>
<td>67</td>
<td>49</td>
</tr>
<tr>
<td>At least 1 recorded</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No attempt</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No spontaneous menstruation, no pregnancy status unknown</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentially fertile group (n = 34)</td>
<td>29 (51%)</td>
<td>5 (19%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal menstruation, no attempt at pregnancy</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal menstruation, pregnancy status unknown</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult fertility group (n = 22)</td>
<td>5 (9%)</td>
<td>17 (62%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No spontaneous menstruation, no pregnancy (attempt and failure)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No spontaneous menstruation, pregnancy status unknown</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of pregnancies (n = 67)</td>
<td>53</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of children (n = 49)</td>
<td>39</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt;2,500 g</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RT = radiotherapy.
on fertility. According to Critchley et al. (11), doses of between 14 and 30 Gy can impair uterine function. This impairment takes the form of reduced uterine volume, reduced elasticity of the uterine musculature, and some uterine vascular damage (12). Along these same lines, in a cohort of 100 female survivors of childhood cancer, transvaginal ultrasonography showed that patients who had been treated with radiation therapy involving the pelvis had a reduced uterine volume that was particularly reduced if the RT was performed before puberty (13). It appears that estradiol can improve uterine function in women with ovarian failure and reduced uterine volume after pelvic irradiation, as long as the radiation doses are less than 30 Gy and the RT is administered after puberty. Otherwise, the estradiol has no significant effect on uterine size, uterine artery blood flow, or endometrial thickness (13, 14). In our cohort of patients who underwent uterine ultrasonography because they had received clinically relevant radiation doses before puberty, it was observed that a prepubertal configuration of the uterus was found after puberty, even when hormonal treatment was prescribed. Thus radiation damage to the uterus incurred before puberty appears to be irreversible.

Other authors, too, have found abdominal RT in female survivors of childhood cancer to be associated with a significant risk of nulliparity, intruterine growth retardation, miscarriage, and premature delivery (3, 4). In addition, a recent study showed a significant risk of miscarriage in female survivors whose ovarian cortex was included in or near (<5 cm) the irradiation field (5). The offspring of the irradiated female patients in this study also more frequently had a birth weight of less than 2,500 g (5). We likewise found many cases of miscarriage (17 of 67 pregnancies) and a higher rate of premature birth and hypotrophy in comparison with the general population: 22% vs. 7.2% (p = 0.01) and 14% vs. 8% (p = 0.2), respectively (15). Nevertheless, we have to interpret these observations with caution because of the small size of our cohort and because we cannot be sure that our population is identical to the Institut National des Statistiques et de la Recherche Médicale population with respect to important factors such as social class, occupation, and tobacco use. Other radiation-related complications of pregnancy such as uterine disruption have also been described (16). It is of note that 1 patient in our cohort underwent a cesarean section because her obstetrician recognized the possibility of uterine rupture, as indicated by a very thin appearance of the uterine musculature on ultrasound studies; this was confirmed at delivery. The latter finding is in keeping with the presumed reduced distensibility of the uterus, which is thought to be the mechanism responsible for most of the observed uterine problems associated with RT (17).

It is also of note that we did not observe an increased risk of congenital malformations in the offspring of the cohort, in keeping with other authors’ findings (18).

CONCLUSIONS

Our results showed that girls who have abdominal RT that excludes the pelvis can go on to have normal fertility and to become pregnant, depending on the nature of associated treatment, especially chemotherapy with alkylating agents. If the RT includes the pelvis, the subfertility risk increases significantly, but some women can still have successful pregnancies. A dose of 4 Gy to the two ovaries and the uterus appears to be the threshold dose for possible subfertility. If the uterus is directly irradiated, however, pregnancies—though rare—are not impossible, even in female patients treated with doses of up to 25 Gy. It is very important for obstetricians to remain vigilant during all pregnancies in women who have undergone pelvic irradiation to prevent risks to both the mother and her offspring. Delivery by cesarean section seems to be the best choice in such women.

Despite the promising results in our study, a fine balance must nonetheless be struck between the doses delivered to the reproductive organs and the doses delivered to the cancer. If the tumor requires a high radiation dose (>15 Gy), a method of fertility preservation must be proposed to the patient and her parents, such as cryopreservation of the ovarian cortex and translocation of the ovaries. Between 4 and 15 Gy, this possibility has to be discussed depending on age and associated treatment. These options and their feasibility also have to be well explained to the patient and her parents. The prospective determination of the doses to be received by the ovaries and uterus should guide the therapeutic decision-making process.

REFERENCES


