Pregnancies Following High-Dose Cyclophosphamide With or Without High-Dose Busulfan or Total-Body Irradiation and Bone Marrow Transplantation

By Jean E. Sanders, Jennifer Hawley, William Levy, Ted Gooley, C. Dean Buckner, H. Joachim Deeg, Kristine Doney, Rainer Storb, Keith Sullivan, Robert Witherspoon, and Frederick R. Appelbaum

Patients successfully treated with a marrow transplant often have concerns about fertility and pregnancy. This study was performed to determine pregnancy outcome among patients who had received high-dose chemotherapy alone or with total-body irradiation (TBI) and marrow transplantation for aplastic anemia or hematologic malignancy. Records of 1,326 postpubertal and 196 prepubertal patients currently more than 12 years of age after marrow transplant in Seattle from August 1971 to January 1992 were reviewed to determine the patients with normal gonadal function and pregnancies. Among 708 postpubertal women, 110 recovered normal ovarian function and 32 became pregnant. In addition, nine formerly prepubertal girls with normal gonadal function became pregnant. Among 618 postpubertal men, 157 recovered testicular function and partners of 33 became pregnant. An additional two formerly prepubertal men had partners who became pregnant. Forty-one female patients and partners of 25 male patients had 146 pregnancies after transplant. All 76 patients responded to a questionnaire requesting pregnancy history, outcome, infant birth weight, and congenital anomalies information for all clinically recognized pregnancies. There were 115 live births among 146 (79%) pregnancies. Spontaneous abortion terminated four of 56 (7%) pregnancies for 28 female cyclophosphamide (CY) recipients and six of 16 (37%) pregnancies for 13 TBI recipients ($P = .02$). Partners of 28 male CY recipients had four of 62 (6.4%) pregnancies terminate with spontaneous abortion, but there were no spontaneous abortions among eight pregnancies of five TBI recipients’ partners. Preterm delivery occurred for eight of 44 (18%) and five of eight (63%) live births for 24 CY and eight TBI female recipients ($P = .01$). This 25% incidence among all female patient pregnancies is higher than the expected incidence of 8% to 10% ($P = .0001$). The 13 preterm deliveries resulted in 10 low birth weight (LBW) 1.8 to 2.2 kg and three very low birth weight (VLBW) ≤1.36 kg infants, for an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population ($P = .0001$). Twelve of the 13 premature infants survive. Congenital anomalies were seen among two of 52 (3.8%) live-born infants of female and six of 63 (9.5%) live-born infants of male patients, which is not different from the 13% of single congenital anomalies reported for the general population. These data demonstrate that clinically recognized pregnancies among women who have received a marrow transplant incorporating TBI are likely to be accompanied by an increased risk of spontaneous abortion. Pregnancies among all women who received a marrow transplant are likely to be accompanied by preterm labor and delivery of LBW or VLBW babies who do not seem to be at an increased risk of congenital anomalies. However, determination of possible adverse effects of parental exposure to high-dose alkylating agents with or without TBI on children born posttransplant requires longer, additional follow-up.

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THE NUMBER OF long-term survivors continues to increase steadily as the use of marrow transplantation for patients with nonmalignant and malignant disorders increases. The agents most commonly used in transplant preparative regimens include high-dose cyclophosphamide (CY) administered alone or in combination with other alkylating agents or total-body irradiation (TBI), thoraco-abdominal irradiation (TAI), or total lymphoid irradiation. In the nontransplant setting, the frequency of early menopause, azoospermia, and germ cell destruction varies with the type and total dose of alkylating agent or irradiation, as well as patient sex and age of the patient at the time of treatment administration. Since both alkylating agents and irradiation are mutagenic with the potential of injury to germ cell chromosomes, children born to patients who recover gonadal function and fertility may be at increased risk for development of genetic diseases and congenital anomalies. However, children born to long-term survivors of conventional chemotherapy for childhood cancer do not have an increased incidence of congenital anomalies, but survivors who received abdominal irradiation have a higher risk of spontaneous abortions and the babies tend to have lower birth weights. Pregnancies occurring among patients who have received marrow transplantation are limited to case reports that include little information regarding the actual pregnancy and few details regarding the infant other than live birth. The present study was performed to determine the impact of the marrow transplant preparative regimen on pregnancy risks and complications among 76 patients transplanted at a single center. The results of 146 pregnancies in these 76 patients show that congenital anomalies are rare, but women, especially those who received TBI, are at high risk for spontaneous abortion, preterm labor, and delivery of low birth weight (LBW) infants.

SUBJECTS AND METHODS

The medical and long-term follow-up records of 1,522 disease-free survivors following marrow transplant at the Fred Hutchinson Cancer Research Center between August 1971 and January 1992 were reviewed. This group included 1,326 consecutive postpubertal female and male patients and 196 consecutive prepubertal female

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Table 1. Patient Characteristics for Adult Females

<table>
<thead>
<tr>
<th>Preparative Regimen</th>
<th>TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.0 Gy</td>
</tr>
<tr>
<td>No. assessable</td>
<td>103</td>
</tr>
<tr>
<td>Age at transplant (yr)</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>13-58</td>
</tr>
<tr>
<td></td>
<td>14-57</td>
</tr>
<tr>
<td>Years posttransplant</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>1-17</td>
</tr>
<tr>
<td></td>
<td>1-6</td>
</tr>
<tr>
<td>No. with ovarian recovery*</td>
<td>56</td>
</tr>
<tr>
<td>No. pregnant§</td>
<td>25 (3)</td>
</tr>
</tbody>
</table>

* 200 mg/kg.
† BU 16 mg/kg, CY 200 mg/kg.
‡ Ovarian recovery posttransplant defined as spontaneous menstruation and normal LH, FSH, and estradiol levels without hormone supplement.
§ Numbers in parentheses represent additional patients who became pregnant among patients prepubertal (aged 3 to 11) at the time of transplant.

Table 2. Patient Characteristics for Adult Males

<table>
<thead>
<tr>
<th>Preparative Regimen</th>
<th>TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.0 Gy</td>
</tr>
<tr>
<td>No. assessable</td>
<td>109</td>
</tr>
<tr>
<td>Age at transplant (yr)</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>13-52</td>
</tr>
<tr>
<td></td>
<td>13-56</td>
</tr>
<tr>
<td>Years posttransplant</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>1-19</td>
</tr>
<tr>
<td></td>
<td>1-5</td>
</tr>
<tr>
<td>No. with testicular recovery*</td>
<td>67</td>
</tr>
<tr>
<td>No. of partners pregnant†</td>
<td>26 (2)</td>
</tr>
</tbody>
</table>

Dosages are as in Table 1.
* Testicular recovery defined as normal LH, FSH, and testosterone levels with evidence of sperm production.
† Numbers in parentheses represent additional patients whose partners became pregnant among patients prepubertal (aged 3 to 11) at the time of transplant.
‡ One man who received BUCY and one man who received 12.0 Gy TBI had cryopreserved sperm collected and stored before transplant, which was used for posttransplant pregnancy.

and male patients who currently were more than 12 years of age. Posttransplant luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (women), and testosterone (men) levels, as well as menstrual history or semen analysis data, prospectively obtained at the time of annual long-term follow-up evaluations, were used to determine recovery of gonadal function. Female patients were considered to have posttransplant gonadal function recovery when spontaneous menstruation occurred and LH, FSH, and estradiol were normal. Recovered male patients had normal LH, FSH, testosterone, and/or sperm production. The number of postpubertal women and men, their preparative regimens, and gonadal function recovery are shown in Tables 1 and 2. Among prepubertal patients, 23 of 82 (28%) girls and 15 of 114 (13%) boys developed normal gonadal function.

Seventy-six patients or partners of patients who became pregnant after transplant were identified. Each of the 76 individuals responded to a questionnaire regarding details for each clinically recognized pregnancy for which they sought medical attention. Information collected included maternal and paternal medication/drug exposure at time of conception and throughout pregnancy, pregnancy duration, outcome, and complications, delivery complications, infant gestational age, birth weight, neonatal complications, birth defects, and growth of the child. In addition, patients either signed forms to release medical information or sent detailed information from each live birth.

Table 3 details the marrow transplant characteristics of these 76 patients. The transplant preparative regimen for 56 patients transplanted for aplastic anemia was CY 200 mg/kg. Twelve patients transplanted for acute myeloid leukemia received CY 120 mg/kg plus TBI administered as a 10.0-Gy single exposure (two women and two men) or 200 Gy/d for 6 consecutive days (eight women). Four patients transplanted for acute lymphoblastic leukemia received CY 120 mg/kg plus TBI administered as a 10.0-Gy single exposure (two women and one man) or 200 Gy/d for 7 consecutive days (one...
woman). Thirty-one patients with chronic myeloid leukemia received 5 mg/kg dimethylbusulfan, 120 mg/kg CY, plus 10.0 Gy TBI, and one received 16 mg/kg busulfan plus 120 mg/kg CY. Thirty-one lymphoma patients received 120 mg/kg CY plus 2.25 Gy/d TBI for 7 days, and a second lymphoma patient received 16 mg/kg busulfan plus 200 mg/kg CY. All TBI was administered from dual cobalt 60 sources at a dose rate of 5 to 8 Gy/min. Before referral, all leukemic patients had received various doses and schedules of chemotherapy. Details of the marrow grafting procedure, prophylaxis for acute graft-versus-host disease, treatment of acute and chronic graft-versus-host disease, and supportive care have been previously described. Twenty-six of these 76 patients had chronic graft-versus-host disease after transplant. All patients had received marrow transplantation and posttransplant follow-up evaluation according to protocols approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

The relationship between the sex of the patient and the type of transplant preparative regimen received was used to evaluate the impact of the preparative regimen on pregnancy outcome, complications, and infant characteristics. A binomial analysis of the approximation to the binomial distribution where the expected rate was considered a fixed parameter was performed to determine whether the rates of confirmed clinically recognized spontaneous abortion, preterm labor (<37 weeks’ gestation), preeclampsia, LBW (>1.5 to <2.5 kg) and very low birth weight (VLBW) (<1.5 kg), and congenital anomalies differed with respect to patient sex and the preparative regimen received, and from the general population. Depending on the number of subjects, chi-square or Fisher’s exact test was used for these comparisons.

RESULTS

Pregnancy Outcome

Forty-one female patients became pregnant between 0.5 and 17.2 years after transplant, and partners of 35 male patients became pregnant between 0.5 and 18.1 years after transplant (Tables 1 and 2). Of these, nine female and two male patients had been prepubertal at the time of transplant. The median length of time after transplant before first pregnancy for all 76 patients was 8.48 (0.5 to 18.1) years. Among postpubertal CY patients, the median time to first pregnancy was 4.34 (0.5 to 12.45) years for females and 6.57 (1.25 to 15.1) years for males. For TBI recipients, the median time to first pregnancy was 6.6 (1.3 to 15.1) years for females and 10 (6.2 to 12.6) years for males. Female patients were a median of 23.1 (15 to 36.2) years of age at the time of first pregnancy, and male patients were a median of 33 (24.1 to 52.3) years of age.

Among CY recipients, nine female and 11 male patients indicated that contraception was practiced before the first pregnancy after transplantation, and one female TBI recipient practiced contraception.

Female patients. Forty-one of these women had a total of 72 pregnancies (Table 4). Among CY recipients, 12 of 56 (21%) pregnancies resulted in early termination because of tubal pregnancy (n = 3) or spontaneous (n = 4) or elective (n = 5) abortion. Elective abortions were performed because of the need to initiate cytotoxic treatment for chronic graft-versus-host disease (n = 1) or by patient request (n = 4). The four clinically recognized spontaneous abortions occurred between 10 and 20 weeks of gestation. There were no gross fetal structural abnormalities reported. The 44 live births were delivered vaginally for 38 and by cesarean section for six. Six women who indicated consumption of less than two alcoholic beverages per week during 12 pregnancies had three abortions (two spontaneous and one elective) and nine live births. One patient indicated that she smoked more than 1 pack of cigarettes per day, and this pregnancy resulted in a live birth. Among TBI recipients, eight of 16 (50%) pregnancies resulted in early termination because of spontaneous (n = 6) or elective (n = 2) abortion. Elective abortions were performed because of a lack of patient desire to be pregnant. There were eight live births, which were delivered vaginally for seven and by cesarean section for one. No alcoholic beverages were reported to be consumed during any of the pregnancies. One woman who smoked less than 1 pack of cigarettes per day had a spontaneous abortion.

The incidence of spontaneous abortions among all female patients was 14%, or 10 of 72 pregnancies (Fig 1). When only female TBI recipients are considered, the incidence of 38% (six of 16) abortions is substantially higher than expected or observed among CY women (P = .02).

Table 4. Pregnancy Outcome After Marrow Transplant

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY TBI</td>
<td>CY BUCY TBI</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>28 13</td>
</tr>
<tr>
<td>Pregnancies (n)</td>
<td>56 16</td>
</tr>
<tr>
<td>Live births (n)</td>
<td>14 8</td>
</tr>
<tr>
<td>(78.5%) (50%) (82.3%)</td>
<td></td>
</tr>
<tr>
<td>Abortions (n)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4 6</td>
</tr>
<tr>
<td>Elective</td>
<td>5 2</td>
</tr>
<tr>
<td>Tubal pregnancy</td>
<td>3 0</td>
</tr>
</tbody>
</table>
Male patients. Partners of 35 male patients had a total of 74 pregnancies. Partners of 28 male CY recipients have become pregnant on 62 occasions. These 62 pregnancies resulted in four spontaneous and seven elective (because of couple desire) abortions and 51 (82%) live births. The method of delivery was vaginal for 46 and Cesarean for five. For 13 of these pregnancies, the mothers indicated consuming an average of two alcoholic beverages per week. These 13 pregnancies resulted in 11 live births and two elective abortions. Three mothers smoked approximately 1 pack of cigarettes per day throughout pregnancy that resulted in three live births and two elective abortions. Two of the men were receiving azathioprine at the time of conception of three pregnancies, all of which resulted in live births.

Partners of two male BUCY recipients became pregnant on four occasions, and partners of five male TBI recipients became pregnant on eight occasions. These 12 pregnancies resulted in 12 live births, all of which were delivered vaginally. None of the mothers of these infants reported alcoholic beverage consumption or cigarette smoking during pregnancy.

The incidence of spontaneous abortion of 11 of 74 (15%) among the partners of all male recipients is not different than the reported incidence of 20% for the general population (P = .121, Fig 1). None of the partners of male TBI recipients reported any abortions.

Pregnancy and Delivery Complications

Female patients. Thirty-two women who became pregnant and did not have the pregnancy terminate early had 24 of 52 (46%) pregnancies accompanied by other complications (Table 5). Eight women who received CY experienced preterm labor and delivery for eight pregnancies. These eight women were a median of 24 (18 to 32) years of age at the time of pregnancy and had been 3.5 to 21 (median, 13.8) years of age when given CY before transplant. Each of five pregnancies of five women given TBI were complicated by preterm labor and delivery. These five women were a median of 23 (18 to 31) years of age at this first pregnancy, which occurred a median of 15 (8 to 21) years after TBI. Preeclampsia with hypertension occurred during four pregnancies of four CY patients and was severe enough to require labor to be induced for two patients. Labor was also induced for one patient with severe hypertension secondary to hyperthyroidism (one pregnancy). Two patients originally transplanted for aplastic anemia developed transient anemia during three pregnancies; the hematocrit, white blood cell count, and platelet count returned to normal following delivery.

Delivery complications occurring among CY recipients included transient maternal hypotension during delivery (one pregnancy), a torn uterus complicating a Cesarean delivery (n = 1), an emergency Cesarean delivery due to fetal distress (n = 1), uterine atony requiring induction of labor (n = 1), and Cesarean delivery of twins in which twin A was 1.95 kg and twin B was 2.5 kg. The only delivery complication among seven TBI pregnancies was a breech presentation.

Male patients. Thirty-five men whose partners became pregnant experienced pregnancy complications for eight of 63 (13%) pregnancies. Two of 63 pregnancies were accompanied by preterm labor (Table 5). Preeclampsia occurred for four partners (6%), who required induction of labor for early delivery because of associated complications. The other pregnancy complications experienced by these partners were first-trimester bleeding, which responded to treatment with bed rest, and hypertension during the last week of two pregnancies. The only delivery complication was a breech presentation.

Preterm labor among the general population is reported to occur in approximately 8% to 10% of pregnancies, and the observed incidence of 13 of 52 (25%) among all pregnancies in women who had received CY or CY plus TBI is significantly greater than expected (P = .001; Fig 2). Among the women, 63% of TBI recipients had preterm labor and delivery, as compared with 20% of CY recipients (P = .017). Four of 52 (7.7%) female patients and four of 63 (6.3%) partners of male patients experienced preeclampsia during pregnancy, which is comparable to the 6% to 8% incidence reported for all pregnancies (female patients, P = .49; male patients, P = .55).

Infants

A total of 115 infants have been born to 67 patients (Table 6).
**PREGNANCIES FOLLOWING MARROW TRANSPLANTATION**

Incidence of patients or reported expected incidence in the white population (P = .0001), and 62.5% for female patients who received TBI v 18% among female CY recipients (P = .17).

**Female patients.** Thirty-nine infants of female patients were 37 to 40 weeks' gestation. One of these infants was small for gestational age (SGA), with a full-term birth weight of 2.4 kg, one of a set of twins had a birth weight of 1.95 kg at 37 weeks, and 37 had birth weights of 2.5 to 4.0 kg (median, 3.35). APGAR scores of these infants were 9 to 10 at 5 minutes after birth.

Thirteen babies were preterm with a gestational age of 24 to 36 weeks (median, 32). Eight of these 13 were born to female CY recipients and five were born to female TBI recipients. Among these 13, 10 with birth weights between 1.8 and 2.4 kg were LBW and three with birth weights between 800 g and 1.36 kg were VLBW. APGAR scores for these infants ranged from 2 to 9 (median, 9) at 5 minutes. One VLBW infant of a TBI female recipient was 24 weeks' gestation, weighed 800 g, and survived for 1 hour after delivery. Eight of the remaining 12 LBW and VLBW babies had multiple neonatal complications including apnea, respiratory distress, hyperbilirubinemia, anemia, and sepsisemia.

These 12 LBW and VLBW infants plus the 39 infants born after at least 37 weeks' gestation currently survive from 1.9 to 19.5 years. None of the infants had major congenital abnormalities. Minor congenital anomalies included multiple congenital nevi (n = 1) and ventricular septal defect (n = 1) among 44 babies born to CY females (4.5%). No genetic abnormalities or congenital anomalies were noted among eight babies born to TBI recipients. No serious or chronic infections or other medical conditions were reported to occur in childhood for any of the babies. Longitudinal growth was appropriate for age and sex of the child (data not shown).

**Male patients.** Among 51 infants born to partners of men who had received CY, 49 had gestational ages between 37 and 40 weeks, and two of these were SGA with birth weights of 2.1 to 2.4 kg. APGAR scores for all 51 babies were 8 to 10 (median, 9) at 5 minutes. The pregnancy history of the parents indicated that both SGA babies were born to the same mother who smoked cigarettes during pregnancy. All eight infants born to partners of men who received TBI and four infants born to partners who received BUCY were at least 37 weeks' gestation and had weight appropriate for gestational age. APGAR scores at 5 minutes were 9 to 10.

No major congenital abnormalities were observed among these children, but minor abnormalities included one with ventricular septal defect, one with congenital hip disease, and four with eczema at birth. Infant growth and childhood infectious diseases were normal and appropriate for age. These children are now 1.0 to 16.0 years of age.

The incidence of 13 of 52 (25%) LBW and VLBW infants among the female patients is significantly higher than the expected incidence of 6.5% reported for the general white population (P = .001; Fig 3). The congenital anomaly incidence of 3.8% (2 of 52) among female patients and 9.5% (6 of 63) among male patients is not greater than the fre-
quency of single anomalies of 13% reported in the general population.

DISCUSSION

The current study was performed to evaluate the effect of marrow transplant preparative regimens on pregnancy outcome following successful treatment of aplastic anemia or hematologic malignancy. Postpubertal recipients of high-dose CY have a high probability of recovery of gonadal function. Some of the recipients who receive TBI also recovered normal gonadal function.\textsuperscript{20,22,29,41} Fertility has been shown to be reduced when alkylating agents are combined with irradiation below the diaphragm.\textsuperscript{3,13,42} This study was not designed to determine the probability of fertility after marrow transplant preparative regimens, but it does provide evidence that individuals exposed to TBI are not inevitably infertile.

The present study evaluated pregnancy outcome among all clinically recognized pregnancies in 146 former marrow transplant patients or their partners. The overall frequency of spontaneous abortion of 9.6% is not different from the 12% risk of recognized spontaneous abortion.\textsuperscript{43} However, this incidence most likely underestimates the actual spontaneous abortion rate, because recall of events that may represent a spontaneous abortion is known to be inaccurate, and the incidence of clinically unrecognized early pregnancy loss among pregnancies detected by human chorionic gonadotropin assay has been found to be approximately 22%.\textsuperscript{36,43} Thus, when all the pregnancies of female patients and partners of male patients are considered, the current data do not suggest that previous therapy results in an increased spontaneous abortion rate.

Several case reports have described the outcome of pregnancies among female marrow transplant recipients.\textsuperscript{16-27} The spontaneous abortion incidence determined from these reports for recipients of high-dose alkylating agents alone was one of nine (11%), which is similar to the spontaneous abortion rate of 7% (4 of 56) observed among female CY recipients in the present study. None of the reported five female recipients of 5- to 8-Gy single exposure TBI or TAI administered at dose rates of 19 to 63 Gy/min had spontaneous abortions, but two of four recipients of 10.0 to 12.0 fractionated TBI administered at dose rates of 2 to 10 Gy/min reported spontaneous abortions.\textsuperscript{22,24,26,27} In the current series, 6 of 16 pregnancies (38%) after 10.0-Gy single exposure or 12 to 14.40 fractionated exposure TBI administered at dose rates of 5 to 8 Gy/min resulted in spontaneous abortion. These apparent differences in abortion rates between lower total dose administered at high dose rates per minute of TBI may reflect underreporting of the abortion rates, since the five previously reported patients were transplanted at four different transplant centers, and the purpose of the articles was to report successful pregnancies after TBI or TAI. Alternatively, the different abortion rates may suggest a true difference in the effect of dose rate on germ cell damage. Female children who had received 20- to 35-Gy abdominal irradiation for Wilms' tumor had an abortion rate of 22%.\textsuperscript{13,14} A similar result has been observed among female survivors of childhood cancer other than Wilms' tumor when abdominal-pelvic radiotherapy was included in the treatment.\textsuperscript{35} No increased frequency of abortions has been observed among adult patients treated with chemotherapy and 38- to 45-Gy total nodal irradiation for Hodgkin's disease.\textsuperscript{35} These reports, unfortunately, did not detail the irradiation dose rates. More information is needed before conclusions regarding the impact of dose rate can be reached.

Pregnancies among our female patients were associated with an increased incidence of preterm labor compared with the expected incidence for the general population. Identifiable medical factors related to preterm labor, not associated with preeclampsia, include multiple gestation, infection, and conditions that distort the uterine cavity.\textsuperscript{36,37} Unusual myometrial stretching and conditions that reduce uterine cavity size or uterine tissue perfusion may trigger the early onset of labor. Irradiation may reduce the elasticity of the uterine musculature and/or produce uterine vascular damage.\textsuperscript{44,45} Because pulmonary muscular arteries have been found to be markedly altered after marrow transplantation, uterine arteries may also be similarly altered (Robert Hackman, personal communication, September 1993). Chronic graft-versus-host disease alters elastic fibers in the skin and vaginal vault.\textsuperscript{20,27} Since only three of nine pregnancies with preterm labor in the current study occurred in women with previous chronic graft-versus-host disease, this is unlikely to represent an associated cause.

The pregnancies were carried to at least 37 weeks' gestation for 82% of female CY recipients, 96% of the partners of male CY recipients, and all partners of male TBI recipients. Only three of eight pregnancies among female TBI recipients reached more than 37 weeks' gestation. Three infants with gestational age of at least 37 weeks were SGA, which could be the effect of maternal cigarette-smoking for two of the babies. Although the number of LBW and VLBW infants was small in this study, the observed high incidence (five of eight pregnancies) among female TBI recipients might be anticipated, based on reports that females who received abdominal irradiation for childhood malignancies have a high proportion of LBW babies.\textsuperscript{13,15}

Minor congenital anomalies were identified in 4.5% (2 of 44) of the infants of CY female patients and in 11.8% (6 of 51) of the infants of the partners of CY male patients, and TBI recipients did not report congenital anomalies in their live-born children. The frequency of minor congenital anomalies identified at birth in the general population is 3.8% to 14.7%.\textsuperscript{40} Minor congenital anomalies have been identified in offspring born to 8.1% of female and 7.9% of male survivors of childhood cancer.\textsuperscript{8,12} The cardiac defects and the congenital hip abnormality in the current study were observed in patients whose only exposure to chemotherapy was CY and 175 mg/m² methotrexate for graft-versus-host disease prophylaxis. Both CY and methotrexate in the doses administered in combination with other agents have been associated with an 8.7% and 11% frequency, respectively, of congenital anomalies among children treated for childhood cancer.\textsuperscript{12} The present data are limited by the small number of children born to marrow transplant patients and the small number of observed congenital anomalies. Hence, a biologically significant change in the mutation rate as manifest by
a change in recognizable single-gene defects would not be recognized due to the small sample size. The effects of irradiation, specifically gamma irradiation and neutron irradiation, on the frequency of mutations among Japanese children exposed to the atomic bombs in Hiroshima and Nagasaki have been evaluated. No evidence was found of an effect of radiation on the frequency of mutation among the children of proximally exposed individuals. However, several investigators have identified mutational injury many years after exposure to gamma or neutron radiation in adult patients given cancer treatment with irradiation therapy, chemotherapy, or both. Because patients in the current study have been evaluated for a relatively short time after irradiation exposure (<20 years), these and the prepubertal patients who develop normal gonadal function after TBI may be at risk for the occurrence of mutational injury. All pregnancies among five females who received TBI while prepubertal terminated with spontaneous abortions, but no information was available regarding the aborted products of conception. This study shows that pregnancies among partners of male patients who received CY or CY plus TBI are unlikely to be adversely affected by the previous treatment. However, all pregnancies among female marrow transplant recipients should be considered high risk. Women who received high-dose alkylating agent chemotherapy with TBI are likely to have an increased incidence of spontaneous abortion. Women treated with high-dose alkylators with or without TBI have an increased incidence of pretterm labor and delivery and LBW babies. However, the infants do not appear to have an increased incidence of congenital anomalies. These observations may reflect deleterious effects of marrow transplant preparative regimens on the uterus and its blood supply through the mechanisms of irradiation and graft-versus-host disease. To date, no unusual sequelae have appeared in children born to parents treated with marrow transplantation. Further longitudinal studies are needed to define any late sequelae developing as a result of parental therapy. In addition, continued follow-up evaluation with pregnancy outcome information among the young children who have received marrow transplants will be needed to determine if any late mutational injury may be detected that could effect their offspring.

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