REGULAR ARTICLE

blood advances

# Conditioning intensity and probability of live birth after blood or marrow transplantation, a BMTSS report

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**Key Points**

- Risk of infertility associated with nonmyeloablative doses of TBI is comparable to the risk with non-TBI conditioning.
- BMT survivors are at a 2-fold higher risk of infertility when compared with their closest-age and same-sex matched siblings.

We examine the impact of conditioning intensity (low intensity: nonmyeloablative/reduced intensity vs high intensity: myeloablative) and total body irradiation (TBI) on the probability of live birth after blood or marrow transplantation (BMT). Study participants were drawn from the BMT Survivor Study (BMTSS) and included 1607 transplant survivors between 1974 and 2014 at age ≤45 years, with survival ≥2 years post-BMT and age at study ≥18 years. Closest-age, same-sex biologic siblings (n = 172) were 1:1 matched with 172 survivors. Survivors and siblings self-reported information on sociodemographic, chronic health conditions, and pregnancies. Within survivor analysis: the association between the primary exposure variable (no TBI/low-intensity conditioning; 200 to 800 cGy TBI/low-intensity conditioning; no TBI/high-intensity conditioning; >800 cGy TBI/high-intensity conditioning) and the odds of no post-BMT live birth were examined using multivariable logistic regression, adjusting for clinical and demographic variables. Median age at BMT was 31 years (IQR, 0 to 45), and median length of follow-up was 14.3 years (IQR, 2.4 to 41.4); 39.3% were autologous BMT recipients, and 46.6% were female. Overall, 120 (8.7%) survivors reported post-BMT live births. Receipt of >800 cGy TBI/high-intensity conditioning (odds ratio [OR], 3.7; 95% CI, 1.9-7.0; ref: no TBI/low-intensity conditioning) was associated with higher odds of reporting no live birth post-BMT. In contrast, 200 to 800 cGy TBI/low-intensity conditioning (OR, 1.3; 95% CI, 0.5-3.3), and no TBI/high-intensity conditioning (OR, 0.9; 95% CI, 0.5-1.7) were at similar risk of reporting post-BMT live birth as no TBI/low-intensity conditioning. Comparison with biologic siblings: Using conditional logistic regression, we found that BMT survivors were more likely to report no live birth (OR, 2.0; 95% CI, 1.2-3.3) compared with siblings. These findings could inform conditioning intensity options for patients wishing to preserve fertility post-BMT.

## Introduction

Over 20 000 blood or marrow transplants (BMTs) are performed in the United States every year.[1,2] Improved therapeutic efficacy, ready availability of a wide variety of stem cell sources, and improved transplant strategies (such as nonmyeloablative and reduced-intensity conditioning) have resulted in an increase in the use of BMT as a curative option for a variety of hematologic malignancies and other life-threatening illnesses.[3] Transplant conditioning regimens often use total body irradiation (TBI) and/or

Submitted 5 October 2021; accepted 23 November 2021; prepublished online on *Blood Advances* First Edition 21 December 2021; final version published online 18 April 2022. DOI 10.1182/bloodadvances.2021006300.

Requests for data sharing may be submitted to Smita Bhatia (smitabhatia@uabmc.edu).

The full-text version of this article contains a data supplement.

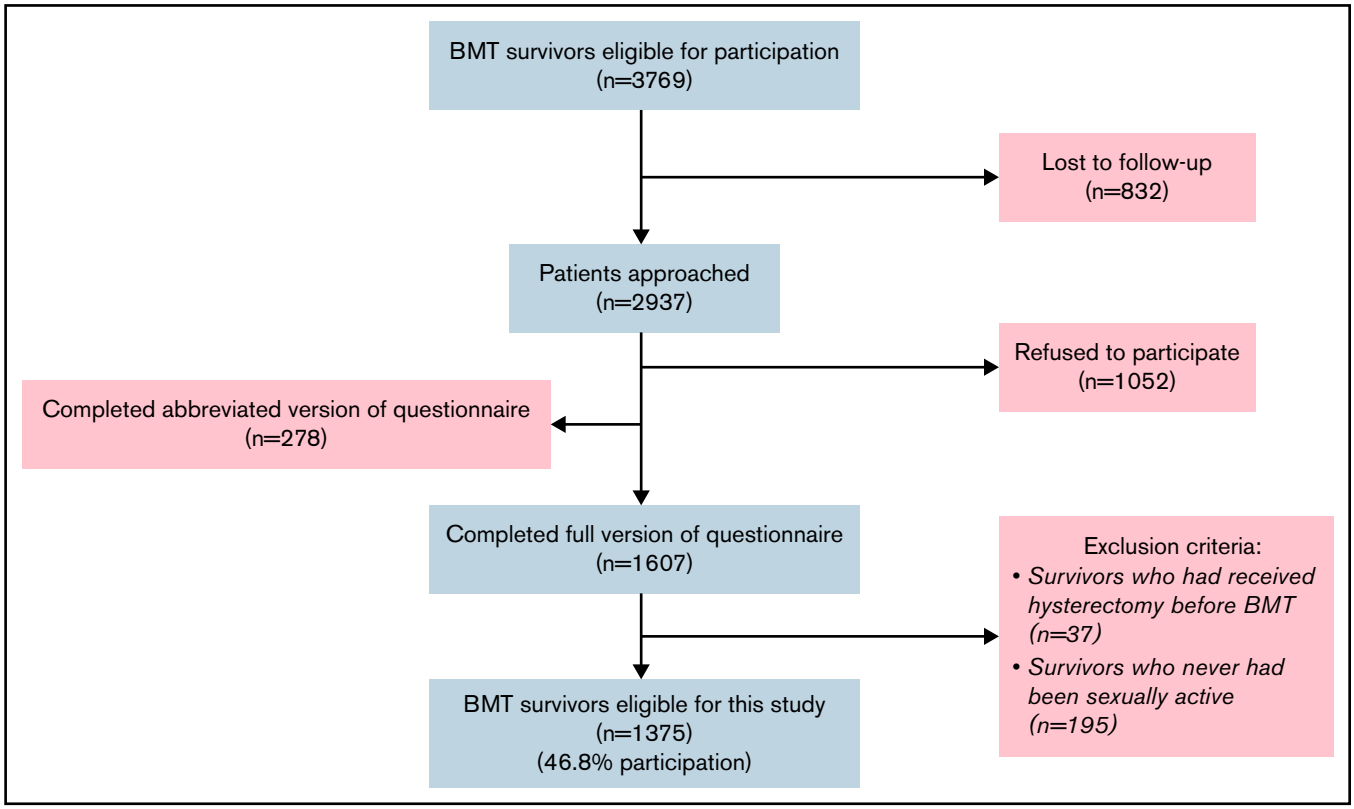


**Figure 1. BMTS survivors' participation flow diagram.**

alkylating agents; both are associated with germ cell injury, gonadal dysfunction, and either transient or permanent infertility.[4-8] The observed interindividual variability in the probability of live birth after BMT is likely dependent on the conditioning intensity (myeloablative condition [high intensity], or nonmyeloablative or reduced-intensity conditioning [low intensity]), age at exposure to gonadotoxic agents, sex of the BMT recipient, as well as post-BMT morbidity (chronic graft-versus-host disease [cGVHD] and other chronic health conditions).[9] While the prevalence of live birth after BMT has been examined previously,[7,10,11] the reports are limited by either small samples or lack of contemporary cohorts and therefore an inability to capture the impact of the newer transplant strategies (eg, conditioning intensity). Finally, the difference in pregnancy outcomes (live births, abortions, and stillbirths) when compared with biologic siblings remains unknown. We addressed these gaps by utilizing the resources offered by the BMT Survivor Study (BMTSS).

## Materials and methods

### Study population

BMTSS is a collaborative effort between the University of Alabama at Birmingham, City of Hope, and University of Minnesota established to examine the long-term outcomes of individuals who have survived 2 or more years after undergoing BMT between 1974 and 2014. BMTSS also examines comparable outcomes in an unaffected comparison group composed of siblings of the BMT survivors. The Institutional Review Board (IRB) at University of Alabama at Birmingham serves as the single IRB of record; the IRBs at University of Minnesota and City of Hope have approved the BMTSS protocol. Participants have provided informed consent according to the Declaration of Helsinki. The present report includes survivors who received BMT at age ≤45 years and were ≥18 years of age at study participation. Participants in the comparison cohort were ≥18 years at study participation.

Study participation consisted of completion of the BMTSS survey designed to capture demographic characteristics and health information. Sociodemographic (race/ethnicity, annual household income, availability of health insurance, level of education), chronic health conditions as diagnosed by the health care provider, and whether the survivors consulted a doctor/took medication to help become pregnant were retrieved from the BMTSS survey. Participants (BMT survivors and siblings) provided a complete reproductive history by supplying details about all pregnancies and their outcomes during their lifetime. Data collected included age at start of each pregnancy and outcome of each pregnancy (ie, whether the pregnancy resulted in a live birth, stillbirth, or abortion [spontaneous or medical]) (supplemental Table 4). Chronic health conditions diagnosed after BMT were graded using the Common Terminology Criteria for Adverse Events, Version 5.0.[12] Survivors' age at BMT, sex, primary diagnosis, type of transplant (autologous; allogeneic), risk of relapse at BMT (standard risk; high risk), conditioning regimens, TBI dose (200 to 800 cGy, >800 cGy) and conditioning intensity (high or low), pre-BMT exposure to pelvic/testicular radiation or alkylating agents, and history of cGVHD were retrieved from the institutional transplant databases and/or participants' medical record.

Of the 3769 BMT survivors eligible for participation, 832 (22.1%) were lost to follow-up. Of the 2937 patients contacted,

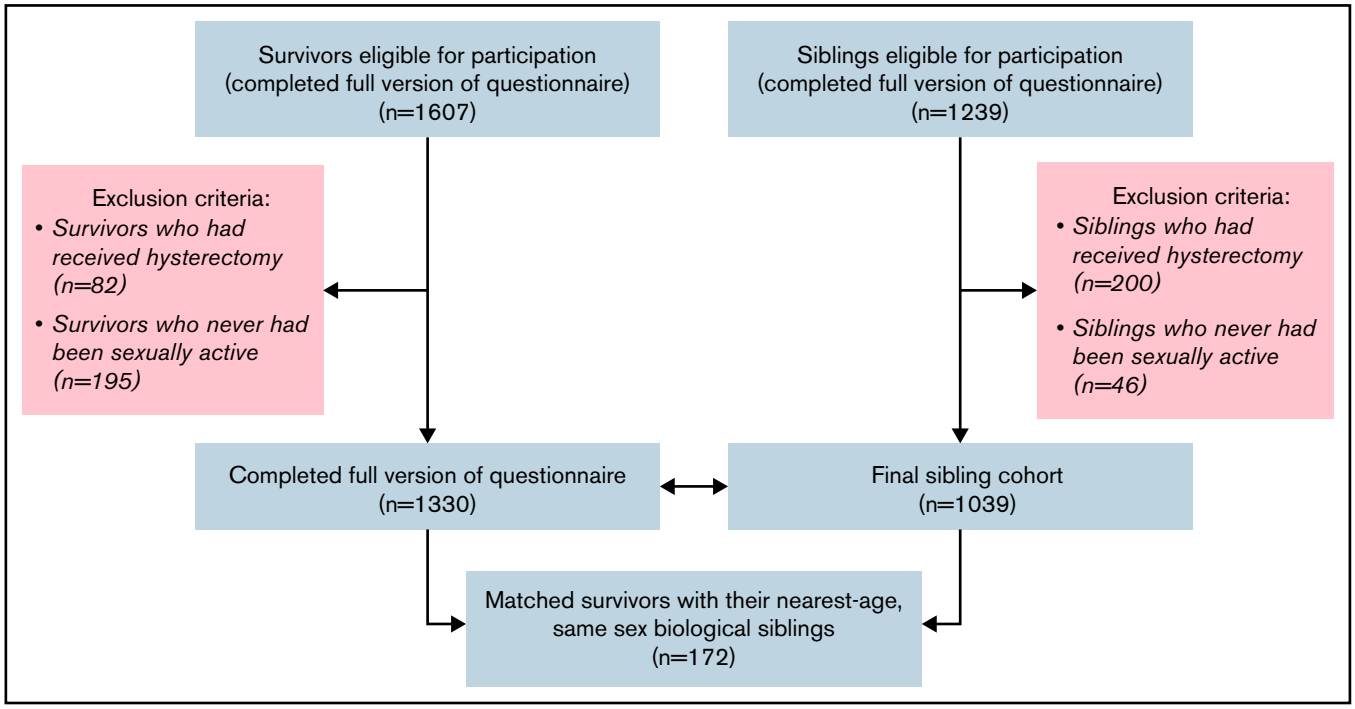


**Figure 2. BMTS sibling and survivor participation flow diagram.**

1052 (33.8%) refused participation, and 278 (9.5%) completed an abbreviated survey that did not include reproductive history. Out of the 1607 participants who completed the full version of the questionnaire, 32 were excluded as they underwent hysterectomy before BMT, and 195 were excluded because they had never been sexually active, yielding 1375 evaluable participants (46.8% of those successfully contacted and meeting inclusion criteria) (Figure 1). When compared with nonparticipants, participants were older at BMT (median age [years]: 31 vs 23), more likely to be female (47.6% vs 39.1%, $P = .004$) and non-Hispanic White (72.5% vs 64.1%, $P < .0001$), more likely to have received conditioning with TBI (57.3% vs 46.6%, $P < .0001$), MAC (80.0% vs 72.8%, $P < .0001$), and more likely to have had a history of cGVHD (48.7% vs 30.5%, $P < .0001$). Participants were less likely to have received conditioning with cytarabine (2.9% vs 4.6%, $P = .03$), melphalan (7.8% vs 14.2%, $P < .0001$), fludarabine (12.3% vs 15.2%, $P = .03$), and cyclophosphamide (66.5% vs 73.1%, $P = .0006$). Participants did not differ from nonparticipants with respect to other conditioning agents or disease status at BMT (supplemental Table 1).

Of the 1239 siblings who completed the full version of the questionnaire, 200 were excluded because they had received a hysterectomy, and 46 were excluded as they had never been sexually active, yielding 1039 evaluable siblings. For the comparison with siblings, we excluded 82 survivors who had received a hysterectomy at any time during their life and 195 who had never been sexually active from the 1607 BMT survivors who had completed the full questionnaire, yielding 1330 survivors. In addition to comparing all evaluable siblings (related or unrelated) with all BMT survivors, we were able to identify 172 survivors matched 1:1 with their nearest-age and same-sex biological sibling to control for genetic or environmental factors that could affect fertility (Figure 2).

***Statistical analysis.*** For bivariate analyses, we used $\chi$-square tests for categorical variables and *t* tests for continuous variables.

WITHIN SURVIVOR COMPARISON. Potential risk factors for not reporting a live birth after BMT were analyzed using multivariable logistic regression. The risk factors examined included age at BMT, sex, race/ethnicity, grade 3 (severe) or grade 4 (life-threatening) chronic health conditions, annual household income, education, type of BMT (autologous or allogeneic), whether the survivor/partner tried for ≥12 months to become pregnant or took medications to help become pregnant, disease status at BMT, history of pelvic/testicular radiation and/or exposure to alkylating agents prior to BMT, and history of live birth prior to BMT. Odds ratio (OR) and associated 95% CI was used to estimate the magnitude of association between the risk of not reporting a live birth and potential risk factors.

BMT survivors were placed into 4 groups based on TBI dose and conditioning intensity: no TBI/low-intensity conditioning (patients who did not receive TBI but received low-intensity conditioning), 200 to 800 cGy TBI/low-intensity conditioning (patients who received 200 to 800 cGy TBI in the context of low-intensity conditioning), >800 cGy TBI/high-intensity conditioning (patients who received >800 cGy TBI in the context of high-intensity conditioning), and no TBI/high-intensity conditioning (patients who did not receive TBI but received high-intensity conditioning).

MATCHED-PAIR COMPARISON WITH BIOLOGIC SIBLINGS. We matched 172 survivors with their closest-age, same-sex biologic sibling, and used conditional logistic regression (adjusted for grades 3 to 4 chronic health conditions, age at study, and history of seeking fertility assistance by consulting a doctor or taking fertility-promoting medications) to determine the magnitude of risk of pregnancy outcomes in BMT survivors when compared with their biologic siblings.

COMPARISON BETWEEN SURVIVORS AND THE SIBLING COMPARISON GROUP. We compared BMT survivors (n = 1330)

**Table 1. Clinical characteristics of survivors with and without live birth after BMT**

| Variables of interest | Post-BMT live birth | | *P* value |
|---|---|---|---|
| | Yes n = 120, (%) | No n = 1255, (%) | |
| **Sex** | | | |
| Female | 52 (43.3) | 589 (46.9) | .5 |
| **Age at BMT in years** | | | |
| <11 | 12 (10.0) | 103 (8.2) | <.0001* |
| 12-24 | 44 (36.7) | 279 (22.2) | |
| 25-34 | 50 (41.7) | 338 (27.0) | |
| >35 | 14 (11.7) | 535 (42.6) | |
| **Follow-up since BMT in years** | | | |
| Median (IQR) | 16.4 (4.3-39.9) | 14.1 (2.4-41.4) | .005* |
| **Age at survey in years** | | | |
| Median (IQR) | 42 (23-66) | 47 (18-73) | .0004* |
| **Race\ethnicity** | | | |
| Non-Hispanic White | 91 (75.8) | 903 (72.1) | .5 |
| Hispanic | 18 (15.0) | 189 (15.1) | |
| Other† | 11 (9.2) | 161 (12.9) | |
| **BMT type** | | | |
| Autologous BMT | 49 (40.8) | 492 (39.2) | .7 |
| **Diagnosis** | | | |
| HL/NHL | 49 (40.8) | 400 (31.9) | <.0001* |
| ALL/AML/MDS | 25 (20.8) | 479 (38.2) | |
| SAA | 23 (19.2) | 70 (5.58) | |
| Other‡ | 23 (19.2) | 306 (24.4) | |
| **Conditioning regimen** | | | |
| TBI | 45 (37.5) | 740 (58.9) | <.0001* |
| Cyclophosphamide | 92 (76.7) | 814 (64.9) | .01* |
| Nitrosoureas | 21 (17.5) | 130 (10.4) | .02* |
| Etoposide | 42 (35.0) | 501 (39.9) | .3 |
| Busulfan | 22 (18.3) | 162 (12.9) | .1 |
| Cytarabine | 2 (1.7) | 37 (2.9) | .4 |
| Melphalan | 5 (4.2) | 99 (7.9) | .1 |
| Fludarabine | 11 (9.2) | 154 (12.3) | .3 |
| **Conditioning intensity** | | | |
| Low-intensity conditioning | 27 (24.8) | 185 (16.7) | .03* |
| High-intensity conditioning | 82 (75.2) | 923 (83.3) | |
| **Total Body Irradiation dose, cGy/Condition intensity§** | | | |
| No TBI/low-intensity conditioning | 19 (17.8) | 124 (11.5) | <.0001* |
| 200-800 cGy TBI/low-intensity conditioning | 8 (7.4) | 56 (5.2) | |
| No TBI/high-intensity conditioning | 45 (42.1) | 245 (22.8) | |
| >800 cGy TBI/high-intensity conditioning | 35 (32.7) | 650 (60.5) | |
| **cGVHD‖** | | | |
| Yes | 29 (43.3) | 371 (50.5) | .3 |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndromes; NHL, non-Hodgkin's lymphoma; SAA, severe aplastic anemia; TBI, total body irradiation.

*Statistically significant differences between groups.

†Other race included: Asian, African American, American Indian, multiracial, and Pacific Islander.

‡Other diagnosis included: chronic myeloid leukemia, other leukemia, paraneoplastic cerebellar degeneration, dyskeratosis congenita, germ cell tumor, extragonadal, inherited abnormality of erythrocyte differentiation and/or function, medulloblastoma, metachromatic leukodystrophy, MS, PNET, rhabdomyosarcoma, sickle cell disease, scleroderma, and testicular carcinoma.

§High-intensity conditioning = myeloablative intensity conditioning; low-intensity conditioning = nonmyeloablative/reduced-intensity conditioning.

‖cGVHD among patients who received allogeneic transplantation.

¶Participants who sought fertility assistance by consulting a doctor or taking fertility-promoting medications.

Table 1. (continued)

| Variables of interest | Post-BMT live birth: Yes n = 120, (%) | Post-BMT live birth: No n = 1255, (%) | *P* value |
|---|---|---|---|
| **Chronic health conditions** | | | |
| Grade 3 or 4 | 36 (30.8) | 472 (39.2) | .07 |
| **Educational status** | | | |
| >high school education | 101 (84.2) | 1062 (84.9) | .8 |
| **Availability of current health insurance** | | | |
| Health insurance available | 110 (91.7) | 1209 (96.3) | .01* |
| **Annual household income** | | | |
| <$50 000 | 30 (25.0) | 362 (28.8) | .001* |
| $50 000-$100 000 | 29 (24.2) | 358 (28.5) | |
| >$100 000 | 55 (45.8) | 370 (29.5) | |
| Not available | 6 (5.0) | 165 (13.2) | |
| **History of pre-BMT livebirth** | | | |
| Yes | 21 (17.5) | 474 (37.8) | <.0001* |
| **Tried medical intervention to become pregnant** | | | |
| Yes¶ | 53 (44.2) | 254 (20.2) | <.0001* |
| **Disease status at first BMT** | | | |
| High risk | 35 (39.8) | 454 (42.5) | .6 |
| **History of pre-BMT pelvic/testicular radiation** | | | |
| Yes | 1 (0.8) | 25 (1.2) | .3 |
| **Pre-BMT alkylating agents** | | | |
| Yes | 58 (48.3) | 558 (44.5) | .4 |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndromes; NHL, non-Hodgkin's lymphoma; SAA, severe aplastic anemia; TBI, total body irradiation.

*Statistically significant differences between groups.

†Other race included: Asian, African American, American Indian, multiracial, and Pacific Islander.

‡Other diagnosis included: chronic myeloid leukemia, other leukemia, paraneoplastic cerebellar degeneration, dyskeratosis congenita, germ cell tumor, extragonadal, inherited abnormality of erythrocyte differentiation and/or function, medulloblastoma, metachromatic leukodystrophy, MS, PNET, rhabdomyosarcoma, sickle cell disease, scleroderma, and testicular carcinoma.

§High-intensity conditioning = myeloablative intensity conditioning; low-intensity conditioning = nonmyeloablative/reduced-intensity conditioning.

||cGVHD among patients who received allogeneic transplantation.

¶Participants who sought fertility assistance by consulting a doctor or taking fertility-promoting medications.

with the entire sibling comparison group (n = 1039) by using logistic regression to determine the magnitude of difference between survivors and siblings in (1) failure to report live birth and (2) pregnancy outcomes. We adjusted the analysis for sex, race/ethnicity, history of seeking fertility assistance by consulting a doctor or taking fertility-promoting medications, and grades 3 to 4 chronic health conditions.

# Results

## Within survivor comparison

Of the 1375 survivors, 541 were autologous BMT recipients (39.3%), and 641 were female (46.6%). The median age at transplantation was 31 years (IQR, 0-45), and at study participation was 46 years (IQR, 18-73). The median length of follow-up from BMT to BMTSS survey completion was 14.3 years (IQR, 2.4-41.4). The primary indications for BMT included Hodgkin or non-Hodgkin lymphoma (HL/NHL: 32.6%), acute lymphoblastic leukemia/acute myeloid leukemia/myelodysplastic syndrome (ALL/AML/MDS: 26.7%), severe aplastic anemia (SAA: 6.8%), and other diagnoses (23.9%).

One hundred and twenty BMT survivors reported a live birth after BMT (8.7%). Provided in Table 1 are the clinical characteristics of the 120 survivors who reported post-BMT live birth and 1255 survivors who did not. The prevalence of live birth did not vary by sex ($P = .5$), history of pre-BMT pelvic/testicular radiation ($P = .3$), or pre-BMT alkylating agent ($P = .4$) exposure. Multivariable analysis revealed that older age at BMT (>35 years: OR, 3.9; 95% CI, 1.32-11.80; reference: age at BMT <11 years), no medical interventions to facilitate pregnancy (OR, 3.1; 95%CI, 1.97-4.74), and >800 cGy TBI/high-intensity conditioning (OR, 3.7; 95% CI, 1.9-7.0; reference: no TBI/low-intensity conditioning) were associated with not reporting a post-BMT live birth (Table 2; Figure 3).

## Comparison with siblings

***Matched-pair comparison with biologic siblings.*** Compared with their nearest-age and same-sex biologic siblings, BMT survivors did not differ in annual household income, educational status,

**Table 2. Multivariable analysis of risk factors associated with reporting no live birth after BMT**

| Variables | OR (95% CI) |
|---|---|
| **Age at first BMT (reference: <11y)** | |
| 12-24 | 0.7 (0.33-1.54) |
| 25-34 | 0.8 (0.34-1.90) |
| >35 | 3.9 (1.32-11.80)† |
| **Tried medical intervention to become pregnant (reference: yes)** | |
| No* | 3.0 (1.96-4.76)† |
| **Total body irradiation dose. cGy (reference: no TBI/low-intensity conditioning)** | |
| 200-800 cGy TBI/low-intensity conditioning‡ | 1.3 (0.51-3.31) |
| No TBI/high-intensity conditioning‡ | 0.9 (0.47-1.65) |
| >800 cGy TBI/high-intensity conditioning‡ | 3.7 (1.91-7.00)† |

Adjusted for: grades 3 to 4 chronic health conditions, sex, race/ethnicity, diseases status, history of pre-BMT pelvic/testicular radiation, history of pre-BMT alkylating agents, history of seeking fertility assistance to facilitate pregnancy, age at study, and history of pre-BMT live birth.

*Participants who did not seek fertility assistance by consulting a doctor or taking fertility-promoting medications.

†Statistically significant differences between groups.

‡High-intensity conditioning = myeloablative intensity conditioning; low-intensity conditioning = nonmyeloablative/reduced-intensity conditioning.

availability of current health insurance, or history of trying medical interventions to facilitate pregnancy (Table 3). BMT survivors were more likely to report no live birth (56.4% vs 40.1%, $P = .003$) but less likely to report spontaneous abortion (9.9% vs 20.9%, $P = .005$). The prevalence of stillbirth or medical abortion was comparable between survivors and their biologic siblings.

After adjusting for history of trying medical interventions to facilitate pregnancy, grades 3 to 4 chronic health conditions, and age at completing the questionnaire, we found that survivors were 2 times more likely to report no live birth (OR, 2.0; 95% CI, 1.2-3.3) compared with their matched biologic siblings. In contrast, survivors were less likely to report spontaneous abortions compared with their biologic siblings (OR, 0.44; 95% CI, 0.23-0.83) (Table 4).

***Comparison between survivors and siblings.*** In supplemental Table 2, we provide a comparison of the clinical and demographic characteristics between BMT survivors and all siblings (related or unrelated) that served as a comparison cohort. The siblings were older (median age: 57.7 years vs 46 years), and more likely to be female (54.8% vs 45.0%), non-Hispanic White (86.5% vs 71.9%), better educated (>high school education: 89.2% vs 84.7%), have health insurance (97.8% vs 96%), and higher income (annual household >$100 000 [42.7% vs 30.9%]). BMT survivors were more likely not to have tried medical interventions to facilitate pregnancy (77.8% vs 66.9%, $P < .0001$), but were less likely to report pregnancies resulting in live birth (42.6% vs 70.5%, $P < .0001$), spontaneous abortion (14.2% vs 19.5%, $P = .0003$), and medical abortion (10.5% vs 14.0%, $P = .009$), compared with the sibling cohort. Survivors were more likely to have grade 3 or 4 chronic health conditions compared with the sibling cohort (37.7% vs 32.5%, $P = .005$). Multivariable logistic regression (supplemental Table 3) after adjusting for sex, race/ethnicity, grades 3 to 4 chronic health conditions, and history of trying medical interventions to facilitate pregnancy showed that BMT survivors were more likely to report no live birth (OR, 3.0; 95% CI, 2.5-3.6), and were less likely

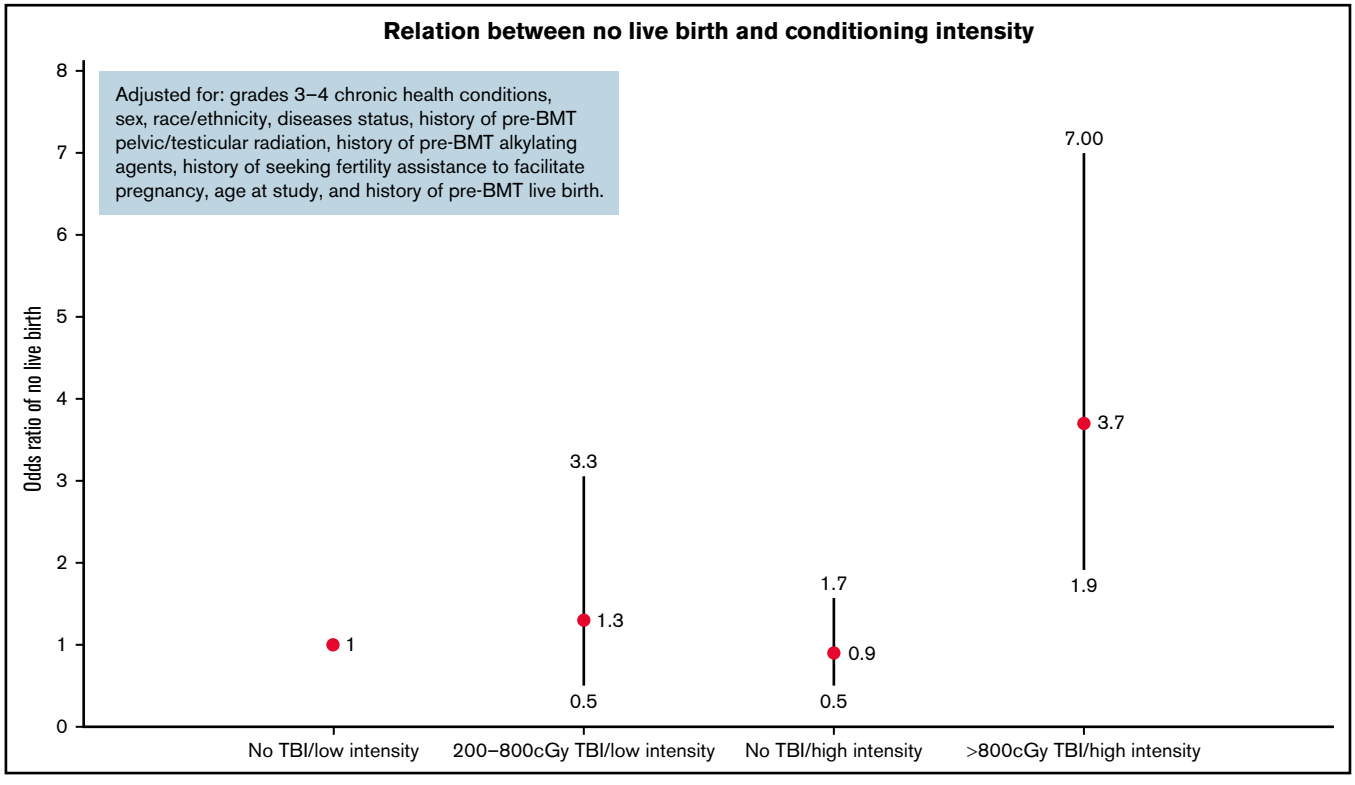


**Figure 3. Odds ratio of no live birth after BMT.**

**Table 3. Characteristics of BMT survivors and matched biological siblings**

| Variables | Survivors n = 172, (%) | Siblings n = 172, (%) | *P* value |
|---|---|---|---|
| Never had a live birth | 97 (56.4) | 69 (40.1) | .003* |
| Ever had still birth | 2 (1.2) | 1 (0.9) | .6 |
| Ever had spontaneous abortion | 17 (9.9) | 36 (20.9) | .005* |
| Ever had medical abortion | 21 (12.2) | 21 (12.2) | 1.0 |
| Tried medical intervention to become pregnant† | 32 (18.6) | 45 (26.2) | .09 |
| **Annual household income** | | | |
| <$50 000 | 48 (27.9) | 34 (19.8) | .3 |
| $50 000-$100 000 | 43 (25.0) | 47 (27.3) | |
| >$100 000 | 63 (36.6) | 76 (44.2) | |
| Do not know | 18 (10.5) | 15 (8.7) | |
| **Educational status** | | | |
| >high school education | 150 (87.2) | 154 (89.5) | .5 |
| ≤high school education | 22 (12.8) | 18 (10.5) | |
| **Availability of current health insurance** | | | |
| Health insurance available | 169 (98.3) | 168 (97.7) | .7 |
| **Total body irradiation dose, cGy/condition intensity‡** | | | |
| No TBI/low-intensity conditioning | 20 (13.2) | – | – |
| 200-800 cGy TBI/low-intensity conditioning | 11 (7.2) | – | |
| No TBI/high-intensity conditioning | 37 (24.3) | – | |
| >800 cGy TBI/high-intensity conditioning | 84 (55.3) | – | |

Matching criteria: closest-age, same-sex biologic sibling.
*Statistically significant differences between groups.
†Participants sought fertility assistance by consulting a doctor or taking fertility-promoting medications.
‡High-intensity conditioning = myeloablative intensity conditioning; low intensity conditioning = nonmyeloablative/reduced-intensity conditioning.

to report spontaneous abortion (OR, 0.7; 95% CI, 0.59-0.92) or medical abortion (OR, 0.7; 95% CI, 0.55-0.94) when compared with the sibling comparison group.

## Discussion

In this study, we found that BMT survivors were 2 times more likely to report no live birth when compared with their biologic same-sex siblings. Nonetheless, 120 BMT survivors reported post-BMT live births, representing 8.7% of the survivor population. Among BMT survivors, the risk for not reporting a live birth after BMT was significantly higher among those who were older at BMT, those who had received >800 cGy TBI in the context of high-intensity conditioning, and those who did not try medical interventions to facilitate pregnancy.

**Table 4. Conditional logistic regression: a comparison of BMT survivors with their matched biological siblings**

| Variables | OR (95% CI) |
|---|---|
| **No live birth** | |
| Biological sibling | reference |
| BMT survivor | 2.0 (1.2-3.3)* |
| **Miscarriage** | |
| Biological sibling | reference |
| BMT survivor | 0.44 (0.23-0.83)* |

Adjusted for grades 3 to 4 chronic health conditions, age at study, and a history of seeking fertility assistance by consulting a doctor or taking fertility-promoting medications.
Matching criteria: closest-age and same-sex biologic sibling.
*Statistically significant differences between groups.

Importantly, there was no difference in the live birth status between patients who did not receive TBI in the setting of high-intensity conditioning and those who received low-intensity conditioning (with or without TBI). Rather, it was the full-dose TBI (in the setting of high-intensity conditioning) that was associated with the lower probability of post-BMT live birth. The association between full-dose TBI and impaired reproductive health is known. Loren and colleagues[8] reported higher pregnancy complications in female allograft recipients compared with a non-BMT population, particularly among those receiving TBI-containing conditioning regimens. However, ours is the first report to find that the probability of live birth among those exposed to low-dose TBI is comparable to patients who received chemotherapy-based high- or low-intensity conditioning.

Similar to this study, previous studies have reported that patients who underwent BMT at a younger age were more likely to report post-BMT live birth[7,10,13,14]; this is consistent with the observed association between increasing age and gonadal dysfunction after BMT.[15,16] Our study found that female survivors or partners of male survivors who tried medical intervention to become pregnant were more likely to report post-BMT live birth when compared with those who did not. Although data on types of medications were not

available, previous studies suggested that survivors benefit from fertility-enhancing interventions.[17]

Comparison with biologic siblings suggested that although survivors were less likely to report live birth compared with their biologic siblings, they were also less likely to report spontaneous abortion. These findings suggest that although the prevalence of live birth is significantly diminished after BMT if pregnancy occurs, the outcome is likely to be favorable.

Findings in this study need to be placed in the context of the limitations. It was difficult to determine the true magnitude of infertility after BMT for a variety of reasons.[11] For example, we did not elicit information regarding attempts at preserving fertility (sperm or oocyte cryopreservation, in vitro fertilization),[18] although we did ask the survivors about needing medications to facilitate pregnancy. Second, we did not have details regarding gonadal dysfunction. Third, we did not elicit information regarding the desire to become pregnant. These limitations notwithstanding, this is the first study to compare reproductive health in BMT survivors to their closest-age, same-sex biologic siblings, allowing us to control for biologic and sociodemographic factors. In addition, this is the first study to examine the impact of conditioning intensity on post-BMT fertility. Pre-BMT counseling to discuss assisted reproductive techniques and sexual health is highly recommended, especially among young patients. Alternative chemotherapeutic regimens with lower doses of TBI could be considered for patients who wish to have children after BMT.

## Acknowledgments

This study was funded by National Cancer Institute, U01 CA213140 and Leukemia Lymphoma Society, and R01CA078938.

## Authorship

Contributions: S.B., S.J.F., D.J.W., S.H.A., and M.A. contributed to study conception and design; S.B., L.H., J.W., E.S., N.B., A.B., H.S.T., L.F., S.H.A., and M.A. collected and assembled the data; N.B. and S.B. analyzed and interpreted the data; N.B. and S.B. drafted the manuscript; S.B., L.H., W.L., J.W., E.S., L.F., and N.B. provided administrative, technical, or material support; S.B., M.A., and S.H.A. supervised the study; and all authors critically reviewed the manuscript for important intellectual content and approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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