

# Reproductive Outcomes After a Childhood and Adolescent Young Adult Cancer Diagnosis in Female Cancer Survivors: A Systematic Review and Meta-Analysis

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Improvements in cancer therapy for childhood and adolescent and young adult (AYA) survivors have increased in excess of 80% among pediatric patients and in excess of 85% among AYA cancer patients. Our research group explored the late effects consequences of cancer treatment on pregnancy and birth outcomes subsequent to a childhood (0–14 years) or AYA (15–25 years) diagnosis of cancer in female cancer survivors. Embase and Medline databases were searched. There were 17 review ( $n = 10$  matched and  $n = 7$  unmatched) studies that met the inclusion criteria. Subanalyses were conducted on 10 matched studies. The median age for all studies for patients at diagnosis and birth was 11 and 27 years, respectively. In matched cohort studies, female childhood and AYA cancer patients, who received chemotherapy alone, had a pooled estimated rate of 18% of experiencing a live birth compared with 10% of females who received radiotherapy alone and subsequently had a live birth. Females who received surgery alone reported higher pooled estimated rates of 44% for a live birth. For matched retrospective review studies, 79% ( $n = 973$ ) of women experienced a live birth, of which 22% of these babies were born preterm. This meta-analysis found lower birth rates for survivors. Access to fertility-related information and discussions around fertility preservation options and oncofertility psychosocial support should be offered to all cancer patients and their families before starting cancer treatment.

**Keywords:** reproduction, pregnancy, birth, survivorship, oncofertility, meta-analysis

## Background

IMPROVEMENTS IN TREATMENT of childhood and adolescent cancers have increased survivorship by 81% among pediatric patients (0–14 years) and 87% among adolescent and young adult (AYA) patients (15–35 years), respectively.<sup>1-4</sup> As a consequence, clinicians are increasingly turning their attention to the late effects of cancer treatment on a survivor's ability to conceive and give birth.<sup>5</sup>

Aggressive cancer therapy required for treatment may result in health-related complications, which may include impaired hormonal responses and infertility.<sup>6-12</sup> The effects of cancer treatment are dependent on a number of variables that include the following: patient's age at diagnosis, the cancer treatment to be administered, and types of chemotherapy drugs and dose and field of radiation administered. Cancer treatment that has the greatest effects on a female's repro-

duction or on the neuroendocrine axis can affect a patient's ability to reproduce in the future compared with other cancers. However, it is also not uncommon for cancer patients to have reduced fertility or infertility at diagnosis as a result of the acute or chronic nature of the cancer itself or as a result of a fertility issue unrelated to their cancer (ovulation problems, endometriosis, polycystic ovary syndrome, etc.).<sup>11</sup>

## Chemotherapy

Individual and combinations of chemotherapy drugs can affect a patient's reproductive health and lead to infertility by causing reduction and damage of ovarian follicles. The impact on a patient's fertility is dependent on a number of factors, including age of a patient at treatment as well as the total cumulative dose of each group of chemotherapeutic agents given. Although there is sufficient information

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available about certain chemotherapy agents, the reproductive effects of combination cancer treatment and new novel drugs remain an area with limited information available.

### Radiotherapy

In females, gonadal damage can be directly effected by radiotherapy treatment, which can cause early depletion of germ cells.<sup>13</sup> The magnitude of risk is related to multiple factors, including age, extent of radiation exposure to the ovaries (field), and total dose given. In general, higher doses of radiation therapy are generally linked to an increased likelihood of infertility.<sup>6,14,15</sup>

Whole abdominal irradiation (total dose is equivalent to 20–30 Gy) results in premature ovarian failure in more than 95% of patients.<sup>16</sup> There have been mixed reports regarding ovarian function following radiotherapy treatment.<sup>17</sup> Radiotherapy can damage the DNA of ovarian follicles, which can eventually lead to a decrease in a patient's ovarian reserve. This may result in women experiencing a decline in the number of ovarian follicles, which may lead to premature menopause.<sup>18</sup>

Studies report that the radiotherapy dose required to irradiate >50% of immature oocytes (lethal dose<sub>50</sub>) is <2 Gy.<sup>19</sup> Other studies report that 20.3 Gy can cause sterilization at birth; 18.4, 16.5, and 14.3 Gy can cause infertility at 10, 20, and 30 years, respectively. This model is used to estimate premature ovarian failure following treatment with radiotherapy.<sup>19,20</sup>

There is also a strong relationship between dose of radiotherapy administered and effects on the pituitary.<sup>21,22</sup> Constine et al.<sup>22</sup> investigated the endocrine effects experienced on female patients after receiving radiotherapy to treat primary brain tumors. Follow-up at <10 years in this cohort of female patients indicated that 70% of women experienced infrequent menstruation (oligomenorrhea), 50% presented with low levels of estradiol (hypopituitarism), and 50% experienced an overproduction of prolactin (hyperprolactinemia).<sup>23</sup>

Bath et al.<sup>24</sup> assessed the hypothalamic–pituitary–ovarian function in female cancer survivors ( $n = 12$ ) who were diagnosed with acute lymphoblastic leukemia and received radiotherapy to the head (prophylactic cranial irradiation). Patients had received doses of radiotherapy of between 18 and 24 Gy (median age at diagnosis = 4.7 years, median age at follow-up = 20.8 years) and were compared with controls without cancer. Outcomes report that cancer survivors experienced a decrease in luteinizing hormone secretion and shorter menstrual cycles compared with controls.<sup>24</sup> Outcomes report that females who receive low-dose prophylactic cranial irradiation may experience premature ovarian failure and may be at greater risk for having a miscarriage.

### Surgery

Surgical procedures to the female gonadal tissue, pelvis, and neuroendocrine axis can also result in infertility and an inability to establish or maintain a pregnancy due to damage to the gonadal organs.

Surgery to the brain can damage the pituitary gland that produces hormones, which has a direct effect on the ovaries responsible for stimulating sex hormone production, as well as egg production.

### Fertility preservation options

Fertility preservation options available for cancer patients are dependent on the age of the patient at cancer diagnosis; type and stage of cancer; urgency of cancer treatment required; and whether the patient has a partner at the time of cancer diagnosis.<sup>14,15,18</sup> Patient access to a reproductive consultation to discuss fertility risks and options in a timely manner has allowed patients the opportunity to preserve their reproductive material before starting gonadotoxic treatment.<sup>25</sup> The guidelines from the American Society of Clinical Oncology,<sup>26</sup> The American Society for Reproductive Medicine,<sup>27</sup> National Comprehensive Cancer Network,<sup>28</sup> and Clinical Oncological Society of Australasia<sup>29</sup> detail that patients must be given an opportunity to consult with a fertility specialist before starting treatment with gonadotoxic therapy, regarding the late effects of fertility-related consequences of cancer treatment and options available for fertility preservation. Studies report that parents and guardians of childhood cancer patients would like to receive oncofertility information and also be given an opportunity to have discussions around the fertility risks and fertility preservation options for their child that may cause psychological distress as an adult cancer survivor.<sup>30</sup>

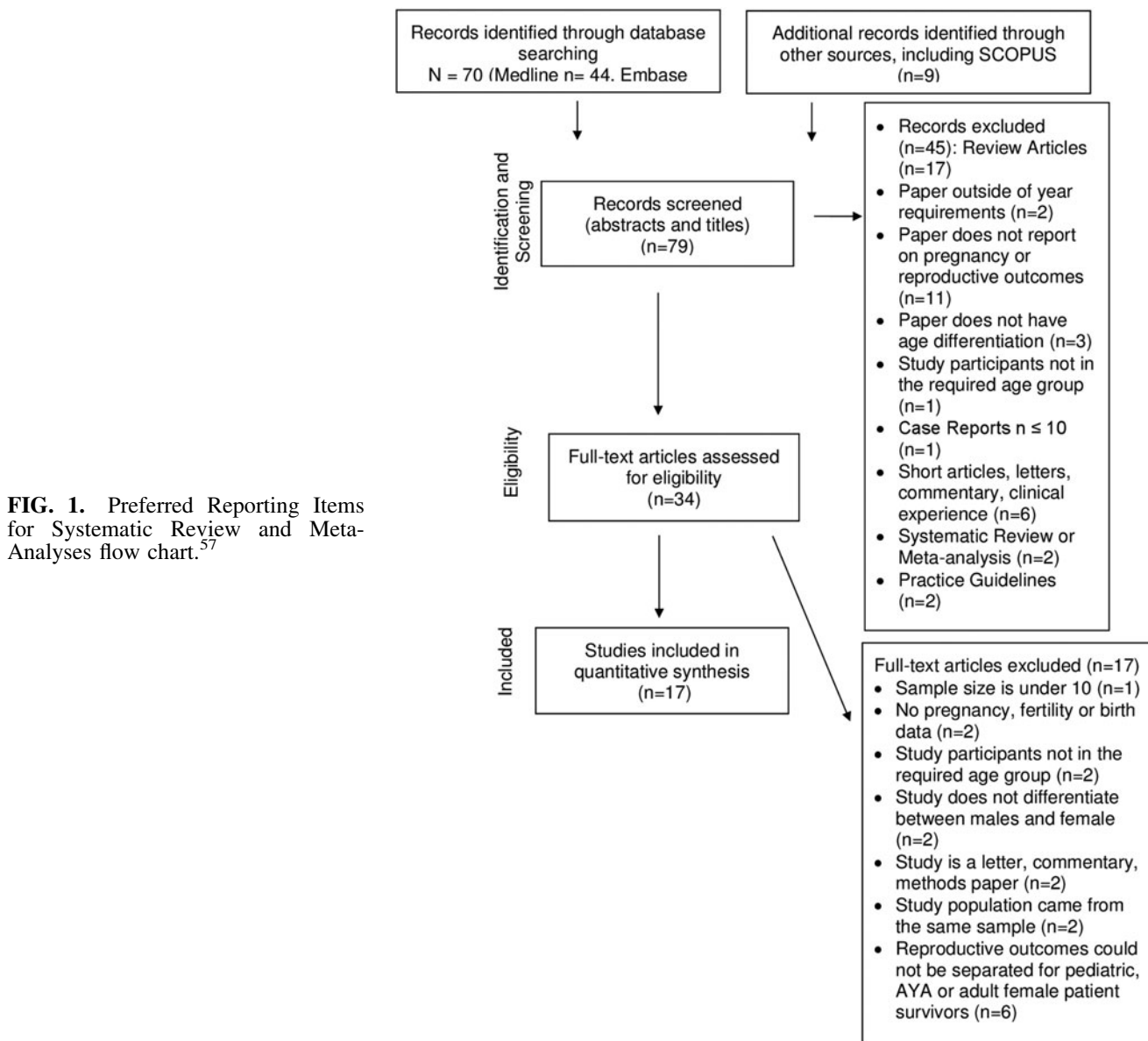
The only available fertility preservation option for prepubescent female cancer patients is ovarian tissue cryopreservation (the collection and storage of tissue from the ovary). Once a patient is ready to have a family in the survivorship period, the cortical ovarian tissue can be reimplanted back into the female patient's pelvis.<sup>31–38</sup> There are several fertility preservation options available for postpubertal female cancer patients and include the following: oocyte cryopreservation (egg collection and storage); embryo cryopreservation; gonadotropin releasing hormone (GnRH analogs)<sup>39–41</sup>; and ovarian transposition (oophoropexy).<sup>42</sup>

As more childhood and AYA cancer survivors reach reproductive age (15–45 years of age), there is a concern that these patients may experience suboptimal fertility or infertility as a late effect consequence of cancer treatment or may be predisposed to poorer maternal and perinatal outcomes, including miscarriage, preterm delivery, low birth weight, and stillbirth.<sup>3,43–51</sup> In addition, cancer survivors may also face several other fertility-related psychological and psychosocial<sup>3,52,53</sup> challenges following cancer treatment, such as uncertainty surrounding their reproductive potential and fears relating to pregnancy and adverse neonatal outcomes.<sup>3</sup>

The aim of this systematic review and meta-analysis was to report on pregnancy and birth outcomes subsequent to a childhood (0–14 years of age) or AYA (15–25 years) cancer diagnosis in female cancer survivors. Results from this study may be beneficial in assisting clinicians with discussing fertility-related options with cancer patients and their families' pre-treatment<sup>54–56</sup> and with providing timely counseling and information to patients about to undergo cancer therapy regarding potential risks of cancer-associated infertility and the benefits of potential fertility preservation options.

### Materials and Methods

This systematic review and meta-analysis was registered with PROSPERO (CRD42017065601) and performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses statement (Fig. 1).<sup>57</sup>



**FIG. 1.** Preferred Reporting Items for Systematic Review and Meta-Analyses flow chart.<sup>57</sup>

We performed a literature search to identify studies that reported on pregnancy and reproductive outcomes following childhood or adolescent young adult cancer treatment. The following databases were searched: Medline (OVID) 1995–September 2016, Embase (OVID) 1995–September 2016. The following keywords were used in the search: “childhood cancer,” “adolescent young adult cancer,” “pregnancy,” “fertility,” “reproductive outcomes,” “birth outcomes,” and “miscarriage.” Both searches were limited to “English language” and “female.” Moreover, we performed a manual search in PubMed of the references cited in the selected articles to search for additional relevant studies, which were then checked in Scopus for additional studies.

Our data search was limited to the following: retrospective studies, population-based studies, cohort studies, case-control studies, randomized control trials, and retrospective review studies. The data collection tool, designed by two of the researchers (A.A., B.G.), was used to screen the papers for inclusion and exclusion eligibility for the review. Abstracts for eligible articles were screened by two of the researchers (B.G.,

S.C.) independently, and the full text for each included study was independently reviewed by four researchers (B.G., A.A., S.C., D.C.).

#### Study inclusion

Studies were included if they met the following criteria: (1) reported on reproductive outcomes following childhood or AYA cancer treatment; (2) published in the English language; (3) population was females diagnosed with childhood or AYA cancer between the ages of 0 and 25 years—if we were unable to discriminate patients between <25 and >25 years, the article was excluded; (4) published in a peer-reviewed journal; (5) had a sample size ≥ 10 patients; and (6) published between January 1, 1995, and September 1, 2016.

#### Data synthesis and analysis

The meta-analysis was conducted using random-effects model with weighted inverse variance methods, as described by DerSimonian-Laird.<sup>58</sup> The Higgins’  $I^2$  test was used to

estimate the approximate proportion of total variability in point estimates that could be attributed to heterogeneity other than that due to chance.

Pooled (combined data for the 10/17 matched studies) reproductive outcome rates and 95% confidence intervals (CIs) are presented to provide an overall estimate of the effect of childhood and AYA cancer treatment on pregnancy and birth outcomes.<sup>59</sup>

## Results

### Study population

Childhood cancer patients were defined as any female patient between the ages of 0 and 14 years and AYA female cancer patients were defined as patients aged 15–25 years. As mentioned previously, any studies where we were unable to discriminate between patients <25 and >25 years were excluded from the analyses.

### Study characteristics

Of the 79 potentially eligible studies, 17 studies met the eligibility criteria to be included in this meta-analysis; four population-based,<sup>4–6,60</sup> six retrospective review studies,<sup>2,61–65</sup> five cohort studies,<sup>66–70</sup> and two surveys.<sup>71,72</sup> The studies were conducted in different geographical regions; six studies were from the Americas (the United States of America and Canada),<sup>6,62,63,67–69</sup> nine from Europe,<sup>4,5,60,64–66,70–72</sup> and one study each from Australasia and the Middle East.<sup>61</sup> Childhood and AYA cancer patients were recruited either via hospital/wards or clinics<sup>2,61–63,65,67,69,70</sup> ( $n=47\%$ ) or from registries<sup>4–6,64,66,68,71,72</sup> ( $53\%$ ).

Approximately, 24,500 cancer survivors had received treatment following a childhood or AYA cancer diagnosis and 42,585 controls were reported in these collective studies, of which 13,929 (57%) female cancer survivors subsequently experienced a live birth. The median age for all female cancer patients at diagnosis was 10.5 years (age range 0–20 years), and the median age for all patients at time of birth was 28 years (age range 22–45 years). Table 1 reports the median age and age range for female cancer survivors at diagnosis and birth, stratified by study design, for the 17 included studies.

Table 2 provides a breakdown of all reported tumor types for the 16 included studies. There was only one study<sup>60</sup> that was not included in this table, as patient diagnoses for both male and female patients were not reported separately. The most commonly reported diagnoses for all studies included solid tumors (26%), leukemia (25%), lymphoma (18%), soft tissue sarcoma (7%), and Wilms tumor (6%).

Table 3 reports reproductive outcomes following cancer treatment received by childhood and AYA female cancer patients for each of the 17 collective studies (matched and non-matched studies).

### Subset analyses

Table 4 and Figures 2 and 3 highlight pooled (combined data for the 10/17 matched studies) reproductive (pregnancy and birth) outcomes following cancer treatment, stratified by study design. We included females from three matched cohort studies<sup>66–68</sup> ( $n=4961$ ), four matched population-based studies<sup>4–6,60</sup> ( $n=7708$ ), and three matched retrospective review studies<sup>61–63</sup> ( $n=5195$ ) in the subset analyses. As data were often reported inconsistently in articles or did not report the type of cancer treatment received, outcomes were only reported where treatment data were available. Our findings reflect lower birth outcomes for cancer survivors, which are reported in the subset analysis.

Preterm was defined as a birth <37 weeks of gestational age.<sup>73</sup>

### Meta-analysis of pregnancy and birth outcomes following treatment modalities for population-based studies<sup>4–6,60</sup>

There were insufficient adjuvant treatment data provided for included population-based studies.<sup>4–6,60</sup> Therefore, we only reported reproductive outcomes where data were available.

Pregnancy data were reported for two<sup>4,6</sup> of the four matched population-based studies, where 44% ( $n=3104$ ) (95% CI: 0.43–0.45;  $I^2=96\%$ )<sup>4,6</sup> subsequently conceived (median age at diagnosis and birth was 12 and 28 years, respectively). Only one study reported data on preterm<sup>5</sup> and live births<sup>6</sup> following cancer treatment, and thus, we were unable to perform subanalysis.

Two population-based studies reported on preterm births, although no gonadotoxic treatment details were provided for these studies.<sup>5,60</sup> A pooled preterm birth rate of 12% ( $n=85$ ) (95% CI: 0.09–0.14;  $I^2=0\%$ ) of babies were born at <37 weeks gestation.

### Meta-analysis of pregnancy and birth outcomes following treatment modalities for cohort studies<sup>66–68</sup>

Treatment with chemotherapy alone. Only one study<sup>67</sup> reported pregnancy data following treatment with chemotherapy alone. Insufficient data were also reported for all other reproductive outcomes (termination, miscarriage, preterm, or stillbirths).

TABLE 1. CHILDHOOD AND ADOLESCENT AND YOUNG ADULT MEDIAN AGE AT DIAGNOSIS AND BIRTH FOR EACH STUDY DESIGN

Age (years)	Population-based studies <sup>4–6,60</sup>	Cohort studies <sup>66–70</sup>	Retrospective review studies <sup>2,61–65</sup>	Survey studies <sup>71,72</sup>
Median age at cancer diagnosis	12	7	11	10
Age range at cancer diagnosis	0–20	0–20	8–24	0–15
Median age at birth	29	27	27	—
Age range at birth	15–44	18–45	18–49	≥ 16

TABLE 2. BREAKDOWN OF ALL REPORTED TUMOR TYPES FOR THE SIXTEEN INCLUDED STUDIES<sup>2,4-6,61-72</sup>

<i>Carcinoma and tumor types</i>	<i>Proportion</i>			
	<i>Number</i>	<i>(%)</i>	<i>Lower</i>	<i>Upper</i>
Acute lymphoblastic leukemia	1239	5	0.05	0.06
Acute myeloid leukemia	6	—		
Breast cancer	3	—		
Cervical cancer	1	—		
Chronic myeloid leukemia	1	—		
Colon	37	—		
Germ cell	191	1	0	0.01
Hodgkin	2676	11	0.10	0.12
Leukemia (general)	4597	20	0.19	0.21
Lymphoma	1445	6	0.05	0.07
Malignant melanoma	25	—		
Neuroblastoma	1090	5	0.04	0.05
Non-Hodgkin lymphoma	1129	5	0.04	0.06
Osteosarcoma	10	—		
Retinoblastoma	420	2	0.01	0.02
Soft tissue sarcoma	1695	7	0.06	0.08
Solid tumor	6162	26	0.25	0.27
Sympathetic nervous system	17	—		
Thyroid cancer	168	1	0	0.01
Urinary cancer	2	—		
Wilms tumor	1515	6	0.06	0.07
Other malignant neoplasms	976	4	0.03	0.05

There was only one study<sup>60</sup> that is not included in this table, as patient diagnoses for both male and female patients were not reported separately.

Three<sup>66-68</sup> matched cohort studies reported live birth outcomes following treatment with chemotherapy alone. For women who conceived, 18% ( $n=224$ ) (95% CI: 0.16–0.20;  $I^2=98\%$ ) experienced a live birth (Fig. 2) (median age at cancer diagnosis and birth was 12 and 23 years, respectively) for these collective studies.

**Treatment with radiotherapy alone.** Three<sup>66-68</sup> matched cohort studies reported on live birth outcomes following treatment with radiotherapy alone. A pooled estimated rate of 10% ( $n=91$ ) (95% CI: 0.08–0.11;  $I^2=80\%$ )<sup>66-68</sup> (Fig. 3) experienced a live birth. Pregnancy data were unavailable for two<sup>66,68</sup> matched cohort studies, and hence, we are unable to determine the actual number of women who successfully conceived and experienced a live birth. The median age reported in the study by Fong et al.<sup>66</sup> at cancer diagnosis and birth was 7 and 30 years, respectively; and for Mueller et al.<sup>68</sup> the median age at diagnosis and birth was 17 and 22 years, respectively. Green et al.<sup>67</sup> provided an age range of 0–20 years at diagnosis, and median age at birth was 23 years. Only one study<sup>66</sup> provided a median time interval of 22 years from end of cancer treatment to birth. Table 3 highlights radiation dose received by cancer patients.

**Treatment with surgery alone.** Two<sup>67,68</sup> of the three matched cohort studies reported data on live births following

treatment with surgery alone. As there was only one<sup>67</sup> study that reported on the number of pregnancies following treatment with surgery alone, birth data provided should be interpreted cautiously as we were unable to determine the proportion of pregnancies that resulted in a birth outcome.

Of the three matched cohort studies, two<sup>67,68</sup> matched cohort studies reported on live births. Of those women who conceived, 44% ( $n=535$ ) (95% CI: 0.41–0.47;  $I^2=98\%$ ) resulted in a live birth.

**Treatment with surgery and chemotherapy.** There was only one<sup>67</sup> study reporting on pregnancy outcomes subsequent to treatment with these combined treatment modalities. Two<sup>67,68</sup> of the three matched cohort studies reported a pooled estimated live birth rate of 20% ( $n=500$ ) (95% CI: 0.18–0.22;  $I^2=99\%$ ).

**Treatment with surgery and radiotherapy.** Similar outcomes were reported for two<sup>67,68</sup> of the three matched cohort studies where 26% ( $n=476$ ) (95% CI: 0.24–0.28;  $I^2=99\%$ )<sup>67,68</sup> (median age at birth was 23 years) experienced a live birth following treatment with these combined therapies. However, there was a lack of data available regarding the dose and field of radiation received, as well as number of conceptions that lead to a subsequent birth.

**Treatment with radiotherapy and chemotherapy.** Three<sup>66-68</sup> matched cohort studies reported an extremely low pooled estimated live birth rate of 14% ( $n=324$ ) (95% CI: 0.13–0.16;  $I^2=99\%$ ) following treatment with combined treatment modalities of radiotherapy and chemotherapy. However, there were no pregnancy data to support how many women conceived, terminated, or experienced a miscarriage following these treatment modalities.

**Treatment with surgery, radiotherapy, and chemotherapy.** Two<sup>67,68</sup> of the three matched cohort studies report a 20% ( $n=921$ ) (95% CI: 0.19–0.22;  $I^2=99\%$ ) live birth rate following multimodality treatments of surgery, chemotherapy, and radiotherapy (age range at diagnosis was 0–20 years, median age at birth was ~23 years). These live birth rates were similar to those reported in survivors who received treatment with surgery followed by radiotherapy.

**Reproductive outcomes for matched cohort studies where no cancer treatment details were reported.** Two matched cohort studies<sup>67,68</sup> reported on stillbirth rates, although specific gonadotoxic treatment data were not reported. Similar stillbirth rates<sup>67,68</sup> were observed for both cancer survivors (0.01%) ( $n=44$ ) (95% CI: 0.00–0.002;  $I^2=0\%$ ) and controls (0.01%) ( $n=106$ ) (95% CI: 0.006–0.01;  $I^2=0\%$ ).

There were slightly more low birth weight babies (<2500 g) reported in cancer survivors (10%) ( $n=275$ ) (95% CI: 0.09–0.11;  $I^2=75\%$ )<sup>67,68</sup> compared with the birth weight of offspring for controls (6%) ( $n=1117$ ) (95% CI: 0.05–0.07;  $I^2=96\%$ )<sup>67,68</sup>. Most offspring for both cancer survivors (80%) ( $n=2301$ ) (95% CI: 0.78–0.81;  $I^2=0\%$ )<sup>67,68</sup> and controls (83%) ( $n=1233$ ) (95% CI: 0.82–0.84;  $I^2=52\%$ )<sup>67,68</sup> were born within a normal birth weight range of 2500–3999 g.

TABLE 3. REPRODUCTIVE OUTCOMES FOLLOWING CANCER TREATMENT RECEIVED BY CHILDHOOD AND ADOLESCENT AND YOUNG ADULT FEMALE CANCER PATIENTS FOR EACH OF THE SEVENTEEN COLLECTIVE STUDIES<sup>2,4,6,60-72</sup> (MATCHED AND NONMATCHED STUDIES)

Author	Age range at diagnosis	Median interval between diagnosis and delivery	Surgery (alone)	Bone marrow transplant (BMT)	Chemotherapy (alone)	Radiotherapy (alone)	Chemotherapy and radiotherapy	Surgery followed by chemotherapy	Surgery followed by radiotherapy	Surgery followed by radiotherapy and chemotherapy	No treatment specified
Cohort studies Fong et al. <sup>66</sup>	Median age: 7 years Range: 0–17 years	22 Years Range: 7–36 years	—	—	Pregnancy: No data provided Live birth: 21/40 (53%)	Pregnancy: No data provided Live birth: 1/40 (3%) Median total cumulative dose: 25.0 Gray (Gy) (range 2.0–40.0 Gy)	Pregnancy: No data provided Live birth: 8/40 (20%)	—	—	—	—
Gawade et al. <sup>69</sup>	Median age: 6 years Range: 0–20 years	—	—	—	Pregnancy: Alkylating score <sup>55</sup> 0 (no alkylators): 1007/1858 (57%) 1: 415/1858 (23%) 2: 254/1858 (14%) 3: 100/1858 (6%) Pregnancy: Anthracycline score 0 (no anthracycline): 1127/1858 (62%) 1: 200/1858 (11%) 2: 302/1858 (17%) 3: 191/1858 (11%)	Radiation to the pituitary pregnancy: 0–2.5 Gy: 1364/1858 (75%) >2.5 Gy: 446/1858 (25%) Radiation to the uterus pregnancy: 0–2.5 Gy: 1703/1858 (92%) >2.5 Gy: 149/1858 (8%) Radiation to the ovaries pregnancy: 0–2.5 Gy: 1666/1858 (92%) >2.5 Gy: 149/1858 (8%)	—	—	—	Pregnancy: No data provided Miscarriage: 397/1858 (21%) Termination: 140/1858 (8%) Live birth: 1300/1858 (70%) Stillbirths: 21/1858 (1%)	
Green et al. <sup>67</sup>	<21 Years	—	Pregnancy: 332/4029 (8%) Live birth: 207/332 (62%)	—	Pregnancy: 154/4029 (4%) Live birth: 91/154 (59%)	Pregnancy: 5/4029 (0.1%) Live birth: 3/5 (60%)	Pregnancy: 370/4029 (9%) Live birth: 230/370 (62%)	Pregnancy: 661/4029 (16%) Live birth: 417/661 (63%)	Pregnancy: 593/4029 (15%) Live birth: 366/593 (62%)	Pregnancy: 1381/4029 (34%) Live birth: 873/1381 (63%)	—
Lantinga et al. <sup>70</sup>	Median age: 7 years Age range: 0–19 years	—	—	—	—	—	—	—	—	—	Pregnancy: 41/124 (33%) Miscarriage: 17/75 (23%) Live birth: 58/75 (77%) Stillbirth: 1/75 (1%)
Mueller et al. <sup>68</sup>	Median age: 17 years Range: 0–19 years	—	Pregnancy: No data provided Live birth: 328/892 (37%)	—	Pregnancy: No data provided Live birth: 112/892 (13%)	Pregnancy: No data provided Live birth: 87/892 (10%)	Pregnancy: No data provided Live birth: 86/892 (10%)	—	Pregnancy: No data provided Live birth: 111/892 (12%)	Pregnancy: No data provided Live birth: 48/892 (5%)	—
Population-based studies Chow et al. <sup>6</sup>	Median age: 12 years Range: 0–20 years Age range: 0–14 years	—	—	—	Pregnancy: 1372/2455 (56%) Live birth: 1143/1372 (83%)	—	—	—	—	—	—
Bhattacharya et al. <sup>60</sup>	Median age: 17 years Range: 0–20 years Age range: 0–14 years	—	—	—	—	—	—	—	—	—	Pregnancy: No data provided Miscarriage: 18/176 Preterm births: 24/176 Birth: 176 (no pregnancy denominated provided)
<i>(continued)</i>											

(continued)

TABLE 3. (CONTINUED)

Author	Age range at diagnosis	Median interval between diagnosis and delivery	Surgery (alone)	Bone marrow transplant (BMT)	Chemotherapy (alone)	Radiotherapy (alone)	Chemotherapy and radiotherapy	Surgery followed by chemotherapy	Surgery followed by radiotherapy	Surgery followed by radiotherapy and chemotherapy	No treatment specified
Madanat-Harjuoja et al. <sup>3</sup>	Range: 0–19 years	—	—	—	—	—	—	—	—	—	Pregnancy: No data provided Preterm birth: 58/546 (11%) Termination: 292/1479 (20%) Pregnancy: 649/1688 (38%)
Winther et al. <sup>4</sup>	Age range: 0–19 years	—	—	—	—	—	—	—	—	—	—
Retrospective review studies Bar et al. <sup>61</sup>	Median age: 11 years Range: 3–18 years	—	—	—	Pregnancy: No data provided Miscarriage: 6/72 (8%) Termination: 9/72 (13%) Preterm birth: 9/63 (14%) Live birth: 63/72 (88%)	—	—	—	—	—	—
Barton et al. <sup>63</sup>	Range: 0–20 years	—	—	Pregnancy: 56/83 (67%)	Pregnancy: 1065/1290 (82%)	Radiotherapy to the uterus/abdomen pregnancy: 670/853 (79%) Radiotherapy to the pituitary pregnancy: 1691/2093 (81%)	—	—	—	—	—
Bessho et al. <sup>2</sup>	Median age: 8 years Range: 5–11 years	—	—	—	—	—	—	—	—	—	Pregnancy: 21/47 (45%) Termination: 5/21 (24%) Live birth: 15/21 (71%) Pregnant: 46/71 (65%) Miscarriage: 5/85 (6%) Termination: 4/85 (5%) Live birth: 59/85 (69%)
Nielsen et al. <sup>64</sup>	—	—	—	—	—	—	—	—	—	—	(continued)

TABLE 3. (CONTINUED)

Author	Age range at diagnosis	Median interval between diagnosis and delivery	Surgery (alone)	Bone marrow transplant (BMT)	Chemotherapy (alone)	Radiotherapy (alone)	Chemotherapy and radiotherapy	Surgery followed by chemotherapy	Surgery followed by radiotherapy	Surgery followed by radiotherapy and chemotherapy	No treatment specified
Signorello et al. <sup>62</sup>	Median: 11 years Range: 0–20 years	—	—	—	Pregnancy: No data provided Preterm birth: 256/1166 (22%) Live birth: 910/1166 (78%)	Pregnancy: No data provided Radiotherapy to the uterus/abdomen: Preterm birth: 252/1116 (23%) Radiotherapy to the uterus/abdomen live birth: 864/1166 (77%) Radiotherapy to the ovary: preterm birth: 172/873 (20%) Radiotherapy to the ovary live birth: 701/873 (80%) Radiotherapy to the ovary: preterm birth: 251/1101 (23%) Radiotherapy to the ovary live birth: 850/1101 (77%)	—	—	—	Pregnancy: No data provided Preterm birth: 441/2201 (20%)	
Sudour et al. <sup>65</sup>	Median: 11 years Range: 0–18 years	—	—	—	—	Abdominal radiotherapy: pregnancy: 53/57 (93%) Abdominal radiotherapy: preterm birth: 3/53 (6%) Abdominal radiotherapy: live birth: 36/53 (68%) Radiotherapy to the ovaries: pregnancy: 14/27 (52%) Radiotherapy to the ovaries: preterm birth: 5/10 (50%) Radiotherapy to the ovaries live birth: 10/14 (71%)	—	—	—	—	
Survey studies Reimuth et al. <sup>72</sup>	Median: 10 years Range: 0–15 years	—	—	—	Pregnancy: No data provided Miscarriage: 247/607 (41%) Live birth: 1035/2998 (34%) Stillbirths: 7/23 (30%)	Pregnancy: No data provided Miscarriage: 333/607 (54%) Live birth: 1632/2998 (54%) Stillbirths: 14/23 (61%)	—	—	—	Pregnancy: 26/330 (8%) Miscarriage: 607/4113 (15%) Termination: 485/4113 (12%) Preterm birth: 368/4113 (9%) Live birth: 2998/4113 (73%) Stillbirths: 23/4113 (0.6%)	
Reulen et al. <sup>71</sup>	—	—	—	—	—	—	—	—	—	—	—

—, no treatment details reported; BMT, bone marrow transplant.



TABLE 4. SUBANALYSES REFLECTING POOLED RATES FOR EACH REPRODUCTIVE OUTCOME, FOLLOWING DIFFERENT CANCER TREATMENT MODALITIES, STRATIFIED BY STUDY DESIGN FOR THE TEN MATCHED STUDIES<sup>2,4-6,60-62,66-68</sup>

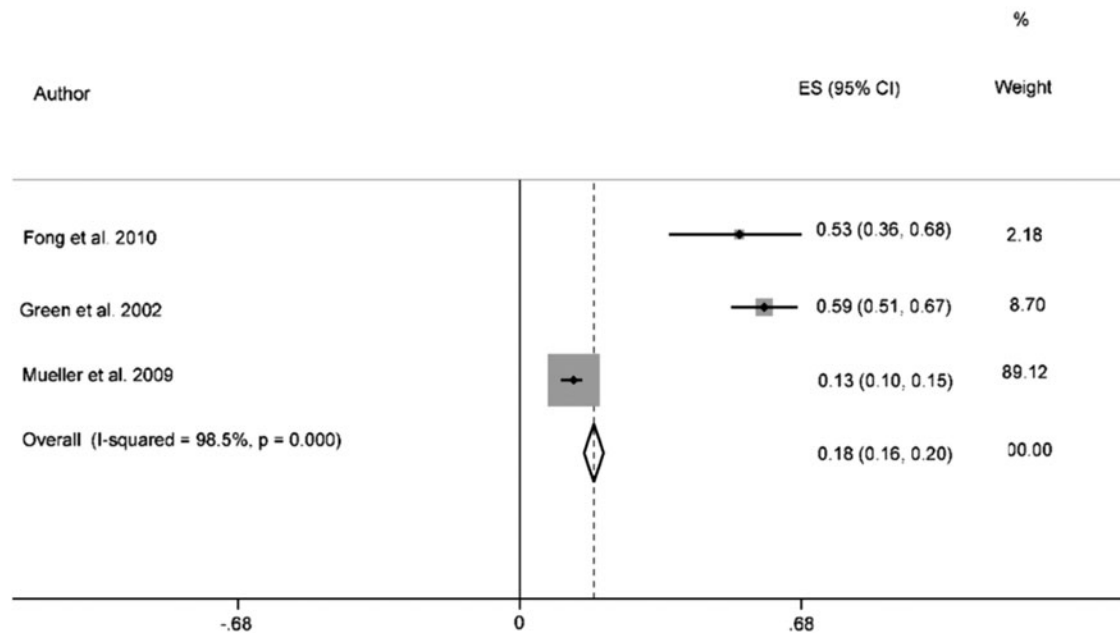
	Radiotherapy (alone)	Chemotherapy (alone)	Surgery (alone)	Chemotherapy and radiotherapy	Surgery followed by chemotherapy	Surgery followed by radiotherapy	Surgery followed by radiotherapy and chemotherapy	No treatment specified
Population-based studies								
Number of women pregnant	—	—	—	—	—	—	—	3104 44% (95% CI: 0.43–0.45; $I^2 = 96\%$ ) <sup>4,6</sup>
Pregnancy rates	—	—	—	—	—	—	—	—
Miscarriage	—	—	—	—	—	—	—	—
Termination	—	—	—	—	—	—	—	—
Number of live births	—	—	—	—	—	—	—	—
Live birth rates	—	—	—	—	—	—	—	—
Number of preterm births	—	—	—	—	—	—	—	85 12% (95% CI: 0.09–0.14; $I^2 = 0\%$ ) <sup>5,60</sup>
Preterm birth rates	—	—	—	—	—	—	—	—
Number of stillbirths	—	—	—	—	—	—	—	—
Stillbirth rates	—	—	—	—	—	—	—	—
Birth weight >2500 g	—	—	—	—	—	—	—	—
Number	—	—	—	—	—	—	—	—
Rate	—	—	—	—	—	—	—	—
2500–3999 g	—	—	—	—	—	—	—	—
Number	—	—	—	—	—	—	—	—
Rate	—	—	—	—	—	—	—	—
Gender at birth	—	—	—	—	—	—	—	—
Male	—	—	—	—	—	—	—	—
Female	—	—	—	—	—	—	—	—
Cohort studies								
Number of women pregnant	—	—	—	—	—	—	—	—
Pregnancy rates	—	—	—	—	—	—	—	—
Miscarriage	—	—	—	—	—	—	—	—
Termination	—	—	—	—	—	—	—	—
Number of live births	91 10% (95% CI: 0.08–0.11; $I^2 = 80\%$ ) <sup>66-68</sup>	224 18% (95% CI: 0.16–0.20; $I^2 = 98\%$ ) <sup>66-68</sup>	535 44% (95% CI: 0.41–0.47; $I^2 = 98\%$ ) <sup>67,68</sup>	324 14% (95% CI: 0.13–0.16; $I^2 = 99\%$ ) <sup>66-68</sup>	500 20% (95% CI: 0.18–0.22; $I^2 = 99\%$ ) <sup>67,68</sup>	476 26% (95% CI: 0.24–0.28; $I^2 = 99\%$ ) <sup>68,68</sup>	921 20% (95% CI: 0.19–0.22; $I^2 = 99\%$ ) <sup>67,68</sup>	—
Live birth rates	—	—	—	—	—	—	—	—
Number of preterm births	—	—	—	—	—	—	—	—
Preterm birth rates	—	—	—	—	—	—	—	44 0.01% (95% CI: 0.00–0.02; $I^2 = 0\%$ ) <sup>67,68</sup>
Number of stillbirths	—	—	—	—	—	—	—	—
Stillbirth rates	—	—	—	—	—	—	—	—

(continued)

TABLE 4. (CONTINUED)

	Radiotherapy (alone)	Chemotherapy (alone)	Surgery (alone)	Chemotherapy and radiotherapy	Surgery followed by chemotherapy	Surgery followed by radiotherapy	Surgery followed by radiotherapy and chemotherapy	No treatment specified
Birth weight >2500 g	—	—	—	—	—	—	—	275
Number	—	—	—	—	—	—	—	10% (95% CI: 0.09–0.11; $I^2 = 75\%$ ) <sup>67,68</sup>
Rate	—	—	—	—	—	—	—	
2500–3999 g	—	—	—	—	—	—	—	2301
Number	—	—	—	—	—	—	—	80% (95% CI: 0.78–0.81; $I^2 = 0\%$ ) <sup>67,68</sup>
Rate	—	—	—	—	—	—	—	
Gender at birth	—	—	—	—	—	—	—	—
Male	—	—	—	—	—	—	—	—
Female	—	—	—	—	—	—	—	—
Review studies	—	—	—	—	—	—	—	—
Number of women pregnant	—	—	—	—	—	—	—	—
Pregnancy rates	—	—	—	—	—	—	—	—
Miscarriage	—	—	—	—	—	—	—	—
Termination	—	—	—	—	—	—	—	—
Number of live births	—	973	—	—	—	—	—	—
Live birth rate	—	79% (95% CI: 0.77–0.80; $I^2 = 77\%$ ) <sup>61,62</sup>	—	—	—	—	—	—
Number of preterm births	—	265	—	—	—	—	—	—
Preterm birth rates	—	22% (95% CI: 0.20–0.24; $I^2 = 65\%$ ) <sup>61,62</sup>	—	—	—	—	—	—
Number of stillbirths	—	—	—	—	—	—	—	—
Stillbirth rates	—	—	—	—	—	—	—	—
Birth weight	—	—	—	—	—	—	—	—
>2500 g	—	—	—	—	—	—	—	—
Number	—	—	—	—	—	—	—	—
Rate	—	—	—	—	—	—	—	—
2500–3999 g	—	—	—	—	—	—	—	—
Number	—	—	—	—	—	—	—	—
Rate	—	—	—	—	—	—	—	—
Gender at birth	—	—	—	—	—	—	—	—
Male	—	—	—	—	—	—	—	—
Female	—	—	—	—	—	—	—	—

—, no treatment details available; CI, confidence interval.



**FIG. 2.** Live births following treatment with chemotherapy (alone) for matched cohort studies.<sup>66–68</sup>

*Meta-analysis of pregnancy and birth outcomes following treatment modalities for retrospective review studies<sup>61–63</sup>*

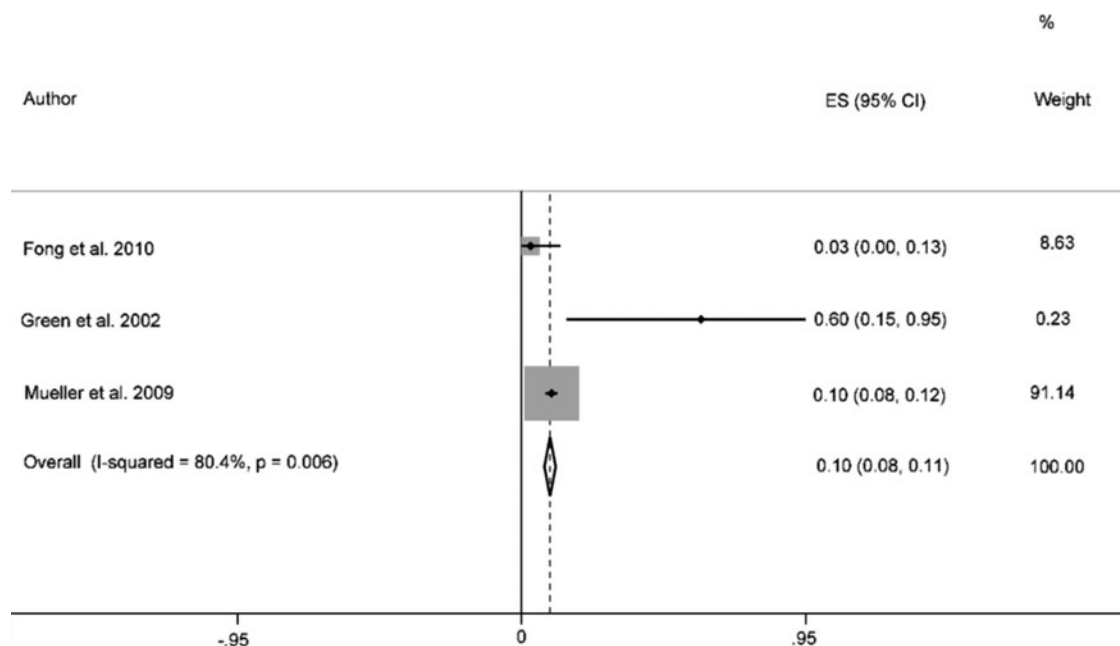
Treatment with chemotherapy alone. Two<sup>61,63</sup> retrospective review studies provided pregnancy outcomes following treatment with chemotherapy alone. Bar et al.<sup>61</sup> did not provide a denominator of all childhood and AYA female patients diagnosed with cancer, only the number of women who became pregnant was reported, and hence, subanalysis could not be conducted.

Of those women who became pregnant, 79% ( $n = 973$ ) (95% CI: 0.77–0.80;  $I^2 = 77\%$ )<sup>61,62</sup> (median age at diagnosis and

birth was 11 and 26 years, respectively) experienced a birth. Of those births, 22% ( $n = 265$ ) (95% CI: 0.20–0.24;  $I^2 = 65\%$ )<sup>61,62</sup> of offspring were born preterm (<37 weeks of gestation).

*There was inconsistent reporting of data regarding all other combination cancer treatments*

**Limitations.** Our study presents a number of limitations that should be considered when interpreting results, with our outcomes based on retrospective published data rather than original patient data. The available information on radiation dose and field and specific chemotherapeutic agents was limited, which may have had an impact on these findings.



**FIG. 3.** Live births following treatment with radiotherapy (alone) for matched cohort studies.<sup>66–68</sup>

Fertility data before a patient starting treatment were not uniformly reported, and hence, we were unable to determine or report whether women had previously reported fertility issues unrelated to their cancer diagnosis and treatment.

In addition, having data available on the number of pregnancies, miscarriages, and terminations would have been useful to determine the actual proportion of live births experienced. Limited information was also available regarding childbearing intent, the number of attempts to initiate a pregnancy, whether a patient underwent fertility preservation before or after treatment, if a patient underwent assisted reproductive technologies following treatment, and gaps regarding length of follow-up from end of treatment to first pregnancy or birth.

## Discussion

This meta-analysis found lower birth rates for survivors. Outcomes from this meta-analysis confirm the importance of fertility discussions and counseling as well as provision of fertility information to be provided before a patient undergoes cancer treatment. Oncofertility psychosocial support should be offered to all cancer patients and their families before starting and following cancer treatment.

In addition, our findings are congruent with current oncofertility guidelines that recommend clinicians have detailed discussions with patients and their families regarding the reproductive risks before starting treatment with gonadotoxic therapy. The American Society of Clinical Oncology recommends that oncologists refer cancer patients to a reproductive specialist for discussion around fertility risks and fertility preservation options before starting cancer treatment.<sup>74</sup> The Australasian Oncofertility Charter,<sup>75</sup> developed by a cancer consumer group in collaboration with cancer and fertility specialists, provides eight key elements of gold standard oncofertility care to provide equitable access to best standard oncofertility care for all cancer patients.<sup>76</sup>

Approximately, 15% of women of reproductive age experience infertility globally. Infertility rates reported in this study for women who have been treated with cancer therapy are considerably higher compared with women from the general population. Previous studies report that female survivors are more than one and a half times more likely to experience clinical infertility compared with their closest aged siblings (relative risk 1.48, 95% CI 1.23–1.78; >1 year of attempts at conception without success)<sup>63</sup> and 8% more likely to experience premature ovarian failure following childhood cancer treatment by the age of 40 years compared with that of a sibling.<sup>63,77</sup>

We performed subanalyses to address pregnancy and birth rates, using data from matched cohort studies,<sup>66–68</sup> population-based studies,<sup>4–6</sup> and retrospective review studies.<sup>61–63</sup> The highest number of live births was reported in the collective matched retrospective review articles, where a pooled estimated rate of 79% of women experienced a live birth (median age at diagnosis and birth was 11 and 26 years, respectively) subsequent to treatment with chemotherapy alone. These rates were four times higher than those female cancer survivors (16%–20%) represented in the matched cohort studies (median age at diagnosis and birth was 12 and 23 years, respectively) who received the same treatment.

However, when interpreting findings for retrospective review studies, it is important to highlight that data reported are

often reliant on self-reported births.<sup>6,78</sup> The authors believe that the disparity in live birth outcomes following treatment with chemotherapy alone for each study design may reflect a form of selection bias referred to as the “healthy mother effect,”<sup>79</sup> that is, where women who subsequently attempt to conceive feel healthier, are less likely to have disease recurrence, and therefore have a better chance for conceiving. The literature also indicates that many childhood cancer survivors self-select to become pregnant, and therefore, outcomes may not reflect a true indication of pregnancy outcomes following treatment.<sup>54,80–83</sup>

As there were limited data available on the number of women who attempted to become pregnant, those who actually became pregnant, the number of women who chose to terminate their pregnancy, and the number of miscarriages experienced, birth data provided should be interpreted cautiously as we were unable to determine the proportion of pregnancies that resulted in a birth outcome.

The literature supports that the overall probability of a first live birth among cancer survivors is lower compared with females from the general population (women without a history of cancer)<sup>84</sup> and that cancer survivors have a lower probability of becoming parents compared with their age-matched comparison group,<sup>84</sup> with pregnancy rates around 40% lower compared with general population rates.<sup>85</sup> Data on the use of specific alkylating agents, particularly the use of new novel agents, cumulative dose, the length of treatment, and age at treatment were not uniformly reported in many of the studies, which are known to cause infertility.<sup>6,86–95</sup> Therefore, we were unable to determine the proportion of women who become infertile as a result of gonadotoxic treatment compared with those women who may have had prior reproductive concerns unrelated to their cancer treatment (e.g., partner infertility, other chronic illness, liver toxicity, autoimmune disease, or fetal chromosomal abnormalities).

The results of three matched cohort studies<sup>66–68</sup> reporting on the outcomes of subsequent births following radiotherapy (alone) report lower pooled estimated live birth rates of between 8% and 11% compared with those women who experienced a live birth following treatment with both surgery and radiotherapy<sup>67,68</sup> (24%–28%) and those patients who received chemotherapy alone. However, as there was a paucity of data regarding the proportion of pregnancies that ended in a miscarriage or were terminated; we were unable to determine the actual proportion of live births that were experienced.

Previous research has highlighted the damaging effects of radiation exposure on gonadal function. Although many studies included in our analysis did not provide sufficient data on radiation dose or site of administration, the literature reports that doses below 4 Gy do not appear to be associated with infertility.<sup>65</sup> Radiation doses of 20 Gy or more to the ovaries and the uterus are more likely to cause infertility.<sup>65,66,96</sup> In addition, the influence of pelvic radiation and spinal radiation (scatter to the uterus) as well as cranial radiation (damage to the hypothalamic–pituitary axis) may also support the possibility for reduced ovarian function and early pregnancy loss.<sup>97</sup>

Cancer survivors are more likely to experience increased anxiety and psychological distress with regard to whether their child might be predisposed to genetic risks.<sup>4</sup> Several studies report that cancer survivors have a strong desire to have a biological family and those who experience cancer-

related infertility are at increased risk for psychological distress.<sup>98</sup> In addition, cancer patients may choose not to start a family due to concerns surrounding a relapse of their cancer, the ability to maintain a health pregnancy, and the potentially increased risks for obstetric and perinatal complications.<sup>3</sup> These concerns may have an impact on the decision of a cancer patient to have children in the future.<sup>84</sup> Some oncologists may choose not to refer patients and their families to a reproductive specialist for discussions around fertility options for reasons associated with uncertainty and knowledge around the types of fertility preservation options available to patients,<sup>99</sup> the emergent need to start cancer treatment, and costs associated with fertility preservation treatment.<sup>100,101</sup>

## Conclusion

This meta-analysis found lower birth rates for cancer survivors. Outcomes from this meta-analysis highlight the importance of offering cancer patients timely access to fertility-related information, as well as discussions around fertility preservation options. Oncofertility psychosocial support should be offered to all cancer patients and their families before starting cancer treatment.

In addition, females should be offered fertility testing, before as well as in the survivorship period to determine the impact that gonadotoxic treatment may have had on a patient's ovarian reserve. Survivors who successfully conceive should be monitored and managed throughout their pregnancy by a multidisciplinary specialist team.<sup>71,102</sup>

## Authors' Contributions

B.G. and A.A. made substantial contributions to the conception and design. B.G., A.A., S.C., and D.C. were accountable for collection and assembly of data. H.W. and B.G. were responsible for data analysis. B.G., A.A., and E.S. were major contributors in drafting and writing the article. All authors read and approved the final article.

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## Author Disclosure Statement

No competing financial interests exist.

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