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Cancer Therapy, Gonadal Function, and Fertility Preservation: Narrative Review

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ABSTRACT

PURPOSE Fertility preservation was designed to help young patients overcome complications of cancer treatments, but its effectiveness is unknown. We sought to investigate how often patients with cancer are offered fertility preservation and if patients offered fertility preservation are more likely to have offspring.

METHODS We searched Embase (through 2022) and PubMed (through 2022). Our broad computerized search strategy was built upon using the keywords "chemotherapy," "radiation," and "fertility." The search took place on December 1, 2022. We included randomized and observational studies and excluded reviews and case reports/series.

RESULTS Eighty-five articles that answered at least one of the research questions were included. Studies assessing fertoprotective therapies often rely on surrogate markers for fertility. Multiple factors affect these markers of fertility. The median premature ovarian failure rate among the intervention group was 18% (IQR, 12%-20%), and among the control group, it was 25% (IQR, 19%-33%). Five of 11 studies reported a significant benefit from fertoprotective therapy. Pregnancies occurred in a median of 21% (IQR, 6%-52%) of patients in the intervention group and 11% (IQR, 7-44) of patients in the control group, with three of seven studies reporting a higher percentage of pregnancies among the intervention group.

CONCLUSION We reviewed the literature on several questions surrounding fertility preservation and found that there is limited and low-quality research on these therapies in cancer. Hence, there is a strong need for studies, especially randomized studies, that follow patients with cancer who undergo fertility preservation and assess outcomes in which patients are most interested.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Cancer therapy frequently results in decreased fertility. About 1 in 10 total cancer cases arise in adults of reproductive age, and the most common cancers in this cohort include breast, bowel, cervical, and testicular.[1] If harm to reproductive organs from therapy is inevitable, preserving gametes, embryos, or tissue may help to preserve fertility.

Both female and male fertility may be impaired after chemotherapy, bone marrow transplant, and/or radiotherapy for cancer. Chemotherapy comprises the largest set of therapies used to treat cancer. Some cancer treatment regimens, historically considered to cause infertility, have had overstated estimates of damage. Researchers have described the reproductive toxicity of frequently used chemotherapy regimens, which can assist with risk stratification before starting therapy, but this has proved to be difficult given the heterogeneity of regimens, patients, and cancers.[2]

Several options are currently available for the preservation of fertility including oocyte cryopreservation, sperm cryopreservation, ovarian tissue cryopreservation, and embryo cryopreservation.[3]

Currently, there is a lack of knowledge about the extent to which cancer therapies affect fertility, which patients choose fertility preservation, and of the patients who do, how successful is the utilization of these products for conception. There is no consistent incidence for infertility after cancer therapy. Furthermore, the degree to which infertility guidance and recommendations are used in clinical practice is unclear.

To tackle gaps in this important topic, we aimed to examine the literature surrounding five key questions: (1) How much

do bone marrow transplant, chemotherapy, and radiation regimens for various cancers affect fertility? (2) What is the rate of referral for fertilization preservation for patients with cancer? (3) How many patients with cancer cryopreserve oocytes, sperm, and embryos? What is the viability of these frozen products? (4) How are oocytes being preserved, and how many oocytes are being preserved? (5) Does fertility preservation result in patients with cancer having more offspring? (6) How effective are fertoprotective therap(ies)? (7) Is there genetic testing for embryos to select nonmutated embryos? To answer these questions, we conducted a narrative review of the published literature.

METHODS

An initial search demonstrated that research studies are too sparse to allow a systemic review and meta-analysis of qualitative research. Therefore, a narrative review commenced.

This narrative review was not preregistered but was conducted in accordance with PRISMA.

Information Sources

We conducted an extensive search for studies reporting on fertility preservation methods in the following databases: Embase (through 2022) and PubMed (through 2022). Our broad computerized search strategy was built upon using the keywords "chemotherapy," "radiation," and "fertility." We filtered to interventional and observational studies. The search took place on December 1, 2022.

We included original article studies evaluating the efficacy of nonsurgical fertility preservation methods. Studies with the following designs were included: (1) randomized controlled trials; (2) controlled clinical trials (ie, experiments in which eligible participants are allocated in a nonrandomized manner to the treatment and the control groups); and (3) other designs, including observational, patient series, prepost studies, and surveys. Only full-length articles or full written reports were considered for inclusion in the review. Studies could be primary or secondary reports of study data.

We excluded studies reporting on surgical fertility preservation methods and surgical sparing practices, studies reported in languages other than English, case reports, case studies, reviews, basic science (cellular) studies, study protocols, and nonempirical studies (eg, commentaries, editorials, government reports) that provided results without strong well-documented statistical assessments.

From review articles that came up in our search, we looked to see if there were other studies that could also be included in our analysis that were not identified in the PubMed and Embase searches.

Study Selection

We independently screened the titles and abstracts and excluded studies that did not match the inclusion criteria. We retrieved full-text articles and determined whether to include or exclude studies on the basis of predetermined selection criteria. We determined whether each article answered one or more of our research questions. In regard to the question on efficacy, we focused on pregnancy (live births), sperm function, and premature ovarian function outcomes. Information obtained from the full-text articles included title, journal/book, question, database found in, tissue, intervention, country, objective(s), setting, patient population, study type/statistical methods used, outcome(s), results (statistics included), conclusions, limitations, study duration, cancer type, publication year, and DOI (Appendix Table A1, online only, not all columns are displayed because of readability). Studies were sorted by question and then subdivided by cancer type, and outcome(s) (eg, hormone level, number of gametes).

In accordance with 45 Code of Federal Regulations §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

RESULTS

Our search resulted in 102 articles on Embase and 1,348 articles on PubMed. After excluding duplicates (n = 3) and articles not meeting eligibility criteria (n = 1,364) and including two articles from review articles, we included 85 articles that answered at least one of the research questions (Fig 1). The median year of publication for all included studies was 2014. Figure 2 shows the number of studies published each year, by review question.

How Do Cancer Treatments Affect Fertility?

Seventeen studies provided estimates on the effect of bone marrow transplant, chemotherapy, and radiation regimens on fertility outcomes in different cancers (Fig 3, Appendix Table A1). Most studies focused exclusively on groups of patients with a specific diagnosis. Of the 17 studies, seven (41%) of the studies assessed fertility in patients with Hodgkin's lymphoma treated with chemotherapy, five (29%) assessed testicular cancer treated with chemotherapy (four articles) or irradiation (one article), three assessed fertility among survivors of leukemia, and two among breast cancer survivors. Measured outcomes serving as surrogate measures for fertility were heterogeneous including semen analysis, ovarian tissue analysis, and hormonal laboratory values.

The results of studies that assessed fertility indicate that patients with cancer face wide variation in outcomes attributable to age at diagnosis, disease, and treatment. However, studies showed that rates of infertility are high among women receiving chemotherapy regimens that

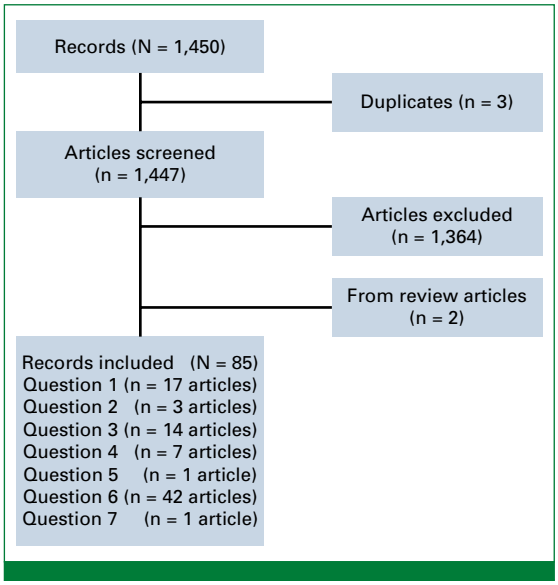

FIG 1. Flowchart of articles identified and included during the systematic search of studies for fertility preservation in patients with cancer.

contain heavy alkylator exposure.[4-7] Dillon et al[7] is one example of how antimullerian hormone measured both before and after treatment can be useful in management of women concerned about fertility potential.

Infertility among men has been less studied, but semen analysis is more reliable compared with markers of ovarian reserve. High follicular stimulating hormone levels are frequently used as indirect markers of fertility dysfunction, but their reliability is questionable.[8]

Although patients with Hodgkin's lymphoma have high overall response rates to therapies, almost 90% of patients develop azoospermia.[8] However, the pretherapy semen quality of patients with cancers such as Hodgkin's lymphoma can be low, with 23% of patients having normozoospermia and 77% of patients having dysspermia.[8] Yet, studies with longer follow-up show that most patients regain normospermic levels within 3-4 months of completing chemotherapy.[9]

What Is the Rate of Referral for Fertility Preservation?

Only two studies assessed rate of referral for fertility preservation.[10,11] Both studies were in concordance with low fertility preservation at medical centers. Surveys from these studies suggest that important discrepancies exist in fertility counseling rates across European countries with rates ranging from 39% to 47% of eligible candidates.[10,11]

How Many Patients With Cancer Cryopreserve Oocytes, Sperm, and Embryos?

Fourteen studies were included in the analysis that examined how many patients underwent fertility preservation.[10,12-18] Heterogeneity among studies was substantial. van der Kaaij et al[19] reported that 40% of men treated for Hodgkin lymphoma cryopreserved sperm before their treatment used. In a 2017 European study that included 38 centers with expertise in children and adolescents, the authors reported that a total of 29% of patients had a fertility preservation procedure performed.[10]

How are Oocytes Being Preserved, and How Many Oocytes Are Being Preserved?

Methods for cryopreserving oocytes include rapid flash cooling with vitrification or controlled slow-freezing. The first successful human birth from a cryopreserved oocyte was reported by Chen in 1986.[20] Oocytes have a low surface area to volume ratio and contain a significant amount of water, placing them at risk for intracellular ice formation.[21] As a result, rapid flash freezing or vitrification has become the primary method of cryopreservation, given its improved success rates compared with slow-freezing.[22] In contrast to slow-freezing where there is a transition from liquid to solid, vitrification consists of a fast solidification process called the glass transition, which preserves the structure of the oocytes causing less spindle damage.[23]

The ideal number of oocytes for cryopreservation has been investigated by various methodologies including mathematical models and cohort studies.[24-26] Among patients younger than 38 years, cryopreserving ≥20 oocytes leads to a 70% chance of one live birth.[25]

Does Fertility Preservation Result in Patients With Cancer Having More Offspring?

Only one study reported the association between increased offspring and fertility preservation. The 2014 study assessed men treated for Hodgkin lymphoma and showed that semen cryopreservation doubled the odds of fatherhood after treatment; with 19% of children conceived using cryopreserved semen.[19] This observational study does, however, suffer from confounding since the report of fatherhood was based on survey response, and there were differences between those who used cryopreservation and those who did not, including education and treatments available at the time of treatment.

How Effective Are Fertoprotective Therap(ies)?

Overall, 42 articles provided estimates on the effectiveness of fertoprotective therapy (Appendix Table A2). Of the 42 studies, 28 articles assessed gonadotropin-releasing hormone agonists (GNRHa), four articles assessed medroxyprogesterone acetate with or without metformin, four articles assessed cryopreservation, three articles assessed tamoxifen, and the remaining three articles assessed other fertoprotective therapies. Only one study evaluated the use and success of the cryopreservation of semen. The most commonly measured outcomes were premature ovarian

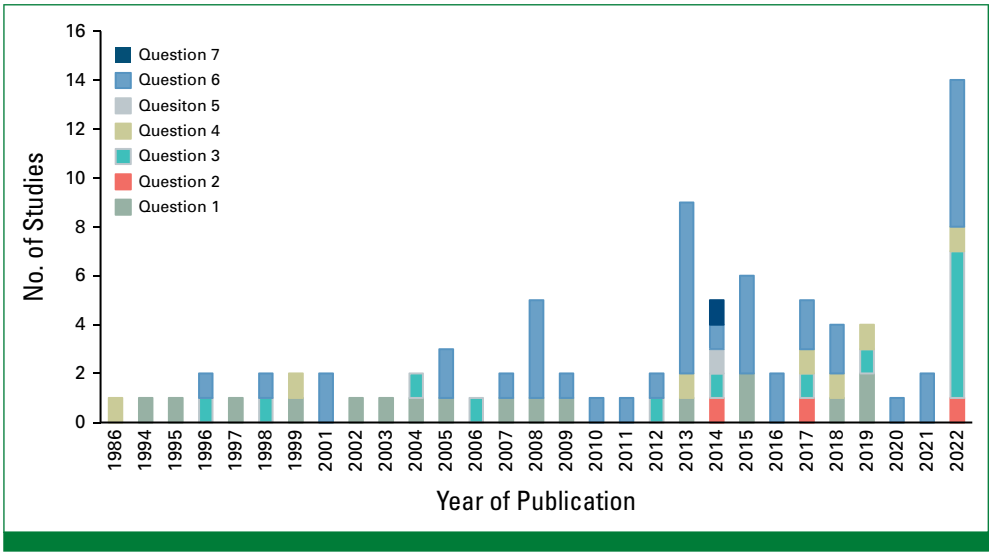

FIG 2. Number of articles, published by year, for each of the five questions in the narrative review of fertoprotective therapies.

insufficiency and post-treatment pregnancy rate. Twenty-one studies were in patients with breast cancer, 10 in lymphoma/leukemia, four in endometrial, and seven in other types of cancer (or general). Fourteen studies were randomly assigned, and 28 were observational.

Among the 14 randomized trials, 11 studies examined premature ovarian failure and eight looked at pregnancy outcomes. Five of 11 studies reported a significant benefit from fertoprotective therapy. Four of 10 randomized studies reported a higher percentage of pregnancies among the intervention group.

Among observational studies, six of the seven studies that compared premature ovarian failure between groups reported significantly lower premature ovarian failure among those using fertoprotective therapy. Five studies looked at pregnancy as an outcome. One reported higher pregnancy rates among individuals receiving therapies, three found no differences, and in another study, it was difficult to determine whether GnRHa was associated with better pregnancy outcome because only six and five people with and without GnRHa therapy planned to have a baby at the time of the study.[27] They found that four of six with GnRHa and two of five without GnRHa resulted in pregnancy. In another study that evaluated cryopreserved semen, researchers found that of those who use cryopreserved semen, 62% of instances led to a pregnancy outcome although there was no comparison group.

Is There Genetic Testing for Embryos to Select Nonmutated Embryos?

Preimplantation genetic testing (PGT) allows examination of single embryo cells for disease, causing gene or chromosomal mutations and subsequent selection of embryos free of the mutations. In the United Kingdom, the Human Fertilisation and Embryology Authority approved the use of PGT for hereditary cancer predisposition genes and diseases (eg, *BRCA1* and *BRCA2* for breast and ovarian cancers, familial adenomatous polyposis, Li-Fraumeni syndrome, neurofibromatosis type 2).[28] Although PGT therapy has been available for decades, there is currently little guidance for its use and controversy given ethical concerns about the selection of embryos.

DISCUSSION

The cost of fertility preservation can be high, as much as $16,000 US dollars (USD) for males[29] and $30,000 USD for women.[30] Considering that there are nearly 70,000 adolescents and young adults who develop cancer each year in the United States,[31] the cumulative costs for these treatments are substantial. As such, the use of fertility preservation should be evidence-based. The gold standard would be proving that fertility preservation results in more offspring years later. These gains exceed any downstream harms, including delays in treatment administration. Our findings indicate that there are limitations in the evidence base, with only one observational study examining the rate of fatherhood with cryopreservation.[19] While this study did find a higher likelihood, it was confounded by differences in education and time period of treatment, and it relied on survey response to determine follow-up status of siring a child.[32] Future research should examine if offering fertility preservation increases progeny and if this varies by age, sex, cancer, and treatment. Who benefits from fertility preservation is largely unknown.

Fertility preservation has large implications. More than 80% of children with cancer become long-term survivors, and fertility is an obvious concern in patients with cancer of

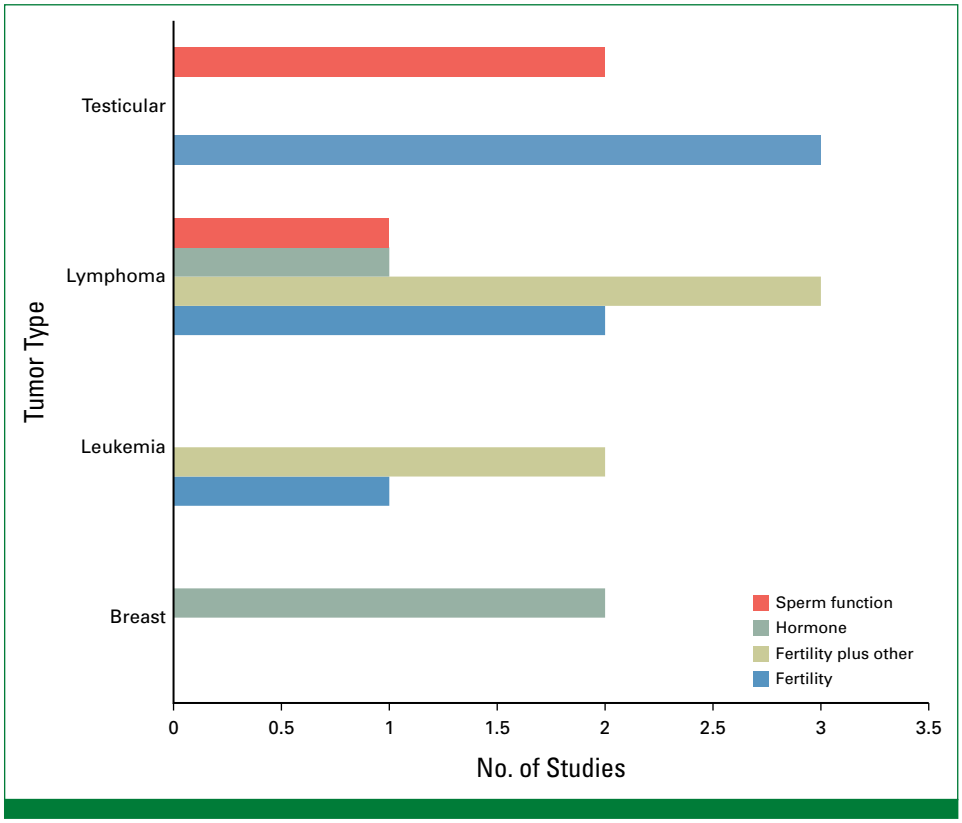

FIG 3. Cancer outcomes assessed for determining the effects of cancer treatment on fertility.

childbearing age.[33] Unfortunately, adolescent and young adult (AYA) patients with cancer have inadequate fertility preservation education. AYA patients with cancer are more likely to either overestimate or underestimate their infertility risk.[34] In addition, young female patients with cancer with nongynecologic cancer have been shown to have a higher risk of subsequent infertility diagnosis.[35] A population study in Ontario, Canada, by Korkdakis et al found that only 4% of females age 15-39 years with newly diagnosed breast cancer were referred for fertility preservation between 2000 and 2017.[36] A recent quality improvement initiative at the Johns Hopkins pediatric oncology clinic created an oncology fertility team that produced improvements in fertility preservation referral rates, although statistical analysis was nonsignificant.[37] Prepubertal female patients with cancer face difficult fertility preservation options as cryopreservation of oocytes is not usually feasible given cancer and the time required for ovarian stimulation. Given the complexity and nuance, in particular, of female AYA patients with cancer, specialized teams, age-appropriate fertility preservation information, and a medical system that supports these patients should be further explored.

The potential effect of cancer therapies on fertility, the use of fertoprotective therapies, referral patterns for fertility preservation, risks of preservation, and disposition of cryopreserved sperm, oocytes, and embryos are all topics requiring more evidence.

The first question of our project aimed to research the effects of different cancer therapies on fertility. The 85 studies found in our narrative review demonstrated that there are a wide variety of effects of cancer therapies (chemotherapy, bone marrow transplant, and radiation) on fertility. Our review yielded a wide array of patient demographics (eg, age, sex), cancers, treatments, site of administration, and doses. With all these very diverse factors, there are innumerable combinations.

Retrospective cohort studies describe the effect of cancer therapies on fertility. Since chemotherapy regimens often consist of multiple drugs, the influence of specific drugs on fertility is difficult to discern. In looking at all studies, though, it did appear that chemotherapy regimens with alkylating agents (represented by cyclophosphamide) posed a strong risk of infertility. We recommend characterization by risk stratification to specify each regimen accurately.[2] In addition, calculating cyclophosphamide equivalent dosing may provide further standardization.[38] Unfortunately, our study reveals that there is significant inconsistency in monitoring the effects of fertility. Poor surrogate outcomes, lack of patient follow-up, and no control groups contribute to ambiguity among the effects of cancer therapies on fertility. With the development of new tools, we hope that it will be much easier to estimate the impact of therapies on fertility.

In this review, we investigated how cancer therapies (chemotherapy, bone marrow transplant, and radiation) affect fertility, but there is an additional possible treatment

modality of cancer surgery. Gynecologic cancers not only involve chemotherapy and radiation but also use fertility-sparing surgery (FSS), which involves possible partial preservation of the cervix, ovaries, and uterus. A recent review by Floyd et al[39] describes the difficulty of analyzing the evidence of fertility after FSS as many studies do not indicate if conceptions are spontaneous or assisted by reproductive technology, and live birth rates of pregnancies do not often take into patients who do not attempt to conceive. The fertility of patients with gynecologic cancers who undergo FSS is a topic that should be further explored.

Consideration of fertility preservation before cancer treatment remains a possibility to maximize the reproductive potential of patients newly diagnosed with cancer. Overall, fertility preservation is understudied, as we found few high quality studies that investigated this topic. From the data we collected, fertility preservation referral rates remain low and the number of cryopreserved fertility products is unknown.

As discussed in-depth in this article, oocyte cryopreservation and embryo cryopreservation are the standard methods for female fertility preservation, but ovarian tissue cryopreservation remains another option. The theoretical advantage of ovarian tissue cryopreservation is the preservation of follicles potentially containing a lot of oocytes. Of note, ovarian tissue cryopreservation is the only option for prepubertal females with cancer. In total, more than 130 live births have been reported from ovarian tissue cryopreservation.[40] In a recent metanalysis, Ní Dhonnabháin et al compared the total number of clinical pregnancies, live births, and miscarriages in women using oocyte, embryo, or ovarian tissue cryopreservation. Their results demonstrated clinical pregnancy rates of 49.0% and 43.8% for oocyte, embryo, and ovarian tissue cryopreservation, but without significant differences.[41] The study deemed utilization rate of cryopreserved fertility products to be between 5% and 10%. Along with ours, this is one of the only attempts to examine all studies on fertility preservation. Unfortunately, many of the underlying studies have weak methodologies with small sample sizes, undocumented cancer diagnoses, and frequently incomplete or inappropriate statistical analysis.

Literature has shown that oncologists lack knowledge about fertility preservation.[42] We postulate that there are significant barriers to fertility preservation given the cost, public perceptions, limited research, and institutional factors such as lack of practice guidelines. Cultural, economic, and religious factors also certainly play a role in determining which patients get referred for cryopreservation, what products are preserved, and where cancer-specific fertility information is available.

Fertoprotective therapy using hormone agonists is one of the more studied topics within the realm of fertility and cancer therapies. Collectively, there is an unclear role of protecting gonadal tissue with GnRHa chemotherapy. Observational studies, with concern for confounding, largely showed benefit in premature ovarian failure, but clinical trials have reported conflicting results, questioning the benefit of fertoprotective therapies with hormone suppression.

While we found some evidence that fertoprotective therapies reduced the likelihood of premature ovarian failure, the evidence for these therapies also leading to a higher likelihood of pregnancy was less clear. Premature ovarian failure was the most commonly studied outcome for these types of therapies, perhaps because it can be easily and objectively measured in all patients in a shorter timeframe and is not affected by as many other factors as pregnancy. People who have premature ovarian failure are less likely to get pregnant but are not unable.[43] Studies assessing the surrogacy of premature ovarian failure for pregnancy outcomes are lacking, and any correlation between these two outcomes is unknown. Future studies on this topic should be conducted, especially in the context of cancer treatment.

In addition to fertoprotective therapies, there are fertoprotective surgical procedures. Ovarian transposition and ovariopexy (or oophoropexy) reposition the ovaries typically away from planned radiation. The reported success of ovarian transposition in preventing ovarian failure has significant variance with study rates between 16% and 90%.[44] As is the theme for much fertility research, data on ovarian transposition remain sparse in part because the procedures are underused. That being said, a recent metanalysis demonstrated that in cervical cancer, ovarian transposition offers significant protection of ovarian function.[45]

Financial and insurance considerations are also an important aspect of fertility preservation as cryopreservation is expensive. Within our review, few articles assessed coverage of cryopreservation. The one exception was the original article by Diesch et al evaluating fertility preservation practices across European Society for Blood and Marrow Transplantation centers in 16 different European countries. Their analysis showed that 55% of fertility preservation cases were covered by the public health systems, the government, or charities; 42% by health insurance companies; and 39% by patients themselves.[10] Health care costs and insurance vary drastically from one country to another and within different states in the United States . Currently, fertility treatment is infrequently covered by insurance, and companies are not required to provide insurance coverage for fertility preservation.[46] Recently, multiple US states have passed legislature requiring insurance coverage for fertility preservation.[47]

There are several strengths and limitations to our review. This is the first review, to our knowledge, to systematically review the questions regarding fertility preservation. We used multiple databases to find a comprehensive list of electronically active articles. We were limited in that studies analyzed had substantial differences in assessed outcomes, which made it difficult to conduct a meta-analysis and calculate pooled estimates. Second, there were few studies published on each of the questions, which limits the generalizability of our findings.

In conclusion, we reviewed the literature on a number of questions surrounding fertility preservation and found that there is limited research on fertility preservation in cancer. Furthermore, there is a strong need for studies, especially randomized studies, that follow patients with cancer who undergo fertility preservation.

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Collection and assembly of data: Christopher O. Eden, Alyson Haslam
Data analysis and interpretation: Christopher O. Eden
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cancer Therapy, Gonadal Function, and Fertility Preservation: Narrative Review

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APPENDIX

TABLE A1. Individual Studies Assessing the Questions of How Cancer Treatments Affect Fertility

Title	Journal	Outcome	Cancer	Publication Year
Age at Birth of First Child and Fecundity of Women Survivors of Childhood Acute Lymphoblastic Leukemia (1987-2007): A Study of the Childhood Cancer Registry of the Rhône-Alpes Region in France (ARCERRA)	Pediatr Hematol Oncol	Fecundity	Acute lymphoblastic leukemia	2015
Gonadal function and fertility after stem cell transplantation in childhood: comparison of a reduced intensity conditioning regimen containing melphalan with a myeloablative regimen containing busulfan	Br J Haematol	Gonadal function and fertility	Acute myeloid leukemia, myelodysplastic syndrome, variety of hematologic and congenital disorders	2015
Individualized Prediction of Menses Recovery After Chemotherapy for Early-stage Breast Cancer: A Nomogram Developed From UNICANCER PACS04 and PACS05 Trials	Clin Breast Cancer	Menses Recovery	Breast Cancer	2019
Pretreatment antimüllerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy	Fertil Steril	Rate of posttherapy ovarian reserve recovery	Breast, leukemia, lymphoma, sarcoma, brain, Wilm's, germ cell	2013
Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG)	Blood	Fertility	Hodgkin lymphoma	2008
Rapid recovery of spermatogenesis after mitoxantrone, vincristine, vinblastine, and prednisone chemotherapy for Hodgkin's disease	J Clin Oncol	Recovery of spermatogenesis	Hodgkin's disease	1997
Evaluation of the efficacy of the VEEP regimen in adult Hodgkin's disease with assessment of gonadal and cardiac toxicity	J Clin Oncol	Sterility, cardiopulmonary damage, and second malignancies	Hodgkin's disease	1995
Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial	Lancet Oncol	Serum antimüllerian hormone and follicle-stimulating hormone measurements	Hodgkin's lymphoma	2018
Gonadal function in males after chemotherapy for early-stage Hodgkin's lymphoma treated in four subsequent trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Etude des Lymphomes de l'Adulte	J Clin Oncol	Fertility	Hodgkin's lymphoma	2007
Impact of cancer chemotherapy before ovarian cortex cryopreservation on ovarian tissue transplantation	Hum Reprod	Ovarian function recovery, ovarian graft survival, and incidence of pregnancy	Hodgkin's lymphoma, non-Hodgkin disease	2019

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TABLE A1. Individual Studies Assessing the Questions of How Cancer Treatments Affect Fertility (continued)

Title	Journal	Outcome	Cancer	Publication Year
Fertility and ovarian function are preserved in women treated with an intensified regimen of cyclophosphamide, adriamycin, vincristine and prednisone (Mega-CHOP) for non-Hodgkin lymphoma	Hum Reprod	Fertility and ovarian function	Non-Hodgkin lymphoma	2005
Testicular function in poor-risk nonseminomatous germ cell tumors treated with methotrexate, paclitaxel, ifosfamide, and cisplatin combination chemotherapy	J Androl	Fertility	Nonseminomatous germ cell tumors	2009
Stage I seminoma of the testis: a bi-institutional retrospective analysis of patients treated with radiation therapy only	BJU Int	Paternity after irradiation	Seminoma of the testis	2003
Effect of low-dose testicular irradiation on sperm count and fertility in patients with testicular seminoma	J Androl	Sperm count and fertility	Seminoma of the testis	1994
No long-term increase in sperm aneuploidy rates after anticancer therapy: sperm fluorescence in situ hybridization analysis in 26 patients treated for testicular cancer or lymphoma	Clin Cancer Res	Sperm aneuploidy rates	Testicular cancer	2004
Treatment outcome, body image, and sexual functioning after orchiectomy and radiotherapy for Stage I-II testicular seminoma	Int J Radiat Oncol Biol Phys	Concerns of fertility	Testicular seminoma	2002
Severe adverse impact on sexual functioning and fertility of bone marrow transplantation, either allogeneic or autologous, compared with consolidation chemotherapy alone: analysis of the MRC AML 10 trial	Cancer	Sexual functioning and fertility	Acute myeloid leukemia	1999
Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer	J Clin Oncol	Pregnancy and fertility preservation	Breast	2014
Obstetric outcome after oocyte vitrification and warming for fertility preservation in women with cancer	Reprod Biomed Online	Pregnancy and fertility preservation	Multiple	2015

TABLE A2. Individual Studies Assessing Question of How Effective Fertoprotective Therapy Is

Title	Journal	Therapy	Cancer	Year	Study Design	Difference Between Groups (POF)
Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a	J Natl Cancer Inst Monogr	GnRH agonist	Lymphoma/ leukemia	2005	Case series	Yes
No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial	J Clin Oncol	GnRH agonist	Lymphoma/ leukemia	2016	Randomized trial	No
Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study	Fertil Steril	GnRH agonist	Breast	2009	Randomized trial	Yes
Ovarian rescue/protection from chemotherapeutic agents	J Soc Gynecol Investig	GnRH agonist	Lymphoma/ leukemia	2001	Prospective observational	Single
GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial	Ann Oncol	GnRH agonist	Breast	2017	Randomized trial	Yes
Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report	Gynecol Oncol	GnRH agonist	Other	2001	Prospective observational	Single
No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group	Ann Oncol	GnRH agonist	Lymphoma/ leukemia	2010	Randomized trial	Not assessed
Gonadotropin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial	Obstet Gynecol	GnRH agonist	Breast	2013	Randomized trial	No
Gonadotropin-releasing hormone agonists cotreatment during chemotherapy in borderline ovarian tumor and ovarian cancer patients	Chin Med J (Engl)	GnRH agonist	Other	2013	Retrospective observational	Yes
Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer	J Clin Oncol	GnRH agonist	Breast	2012	Randomized trial	No

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TABLE A2. Individual Studies Assessing Question of How Effective Fertoprotective Therapy Is (continued)

Title	Journal	Therapy	Cancer	Year	Study Design	Difference Between Groups (POF)
Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma	Fertil Steril	GnRH agonist	Lymphoma/ leukemia	2008	Prospective observational	Yes
Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients	Cancer Res	GnRH agonist	Breast	2018	Randomized trial	Yes
GnRH agonist for the prevention of chemotherapy-induced ovarian failure in lymphoma	J Clin Oncol	GnRH agonist	Lymphoma/ leukemia	2013	Randomized trial	No
Primary hormonal treatment for early endometrial carcinoma	Eur J Gynaecol Oncol	Medroxyprogesterone acetate with or without metformin	Endometrial	1998	Prospective observational	Single
Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study	J Clin Oncol	Letrozole and gonadotropins	Breast	2008	Prospective observational	Single
Protective effect of leuprolide on ovarian function in young women treated with adjuvant chemotherapy for early breast cancer: a multicenter phase II study	J Chemother	GnRH agonist	Breast	2008	Prospective observational	Single
Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy	N Engl J Med	GnRH agonist	Breast	2015	Randomized trial	Yes
Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC)	Breast Cancer Res Treat	GnRH agonist	Breast	2008	Prospective observational	Single
Luteinizing hormone-releasing hormone analogues in the treatment of young women with early breast cancer: long-term follow-up of a phase II study	Int J Oncol	GnRH agonist	Breast	2015	Prospective observational	Single
Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women	J Clin Oncol	Medroxyprogesterone acetate with or without metformin	Endometrial	2007	Prospective observational	Singles
Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer	Ann Oncol	Medroxyprogesterone acetate with or without metformin	Endometrial	2016	Prospective observational	Single

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TABLE A2. Individual Studies Assessing Question of How Effective Fertoprotective Therapy Is (continued)

Title	Journal	Therapy	Cancer	Year	Study Design	Difference Between Groups (POF)
Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial	BJOG	Medroxyprogesterone acetate with or without metformin	Endometrial	2020	Randomized trial	Not assessed
Fertility preservation with ovarian stimulation and time to treatment in women with stage II-III breast cancer receiving neoadjuvant therapy	Breast Cancer Res Treat	Unspecified	Breast	2017	Retrospective observational	Single
Five-year changes in ovarian function restoration in premenopausal patients with breast cancer taking tamoxifen after chemotherapy: An ASTRRA study report	Eur J Cancer	Tamoxifen	Breast	2021	Prospective observational	Single
Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation	J Clin Oncol	Tamoxifen	Breast	2005	Prospective observational	Single
Concomitant tamoxifen or letrozole for optimal oocyte yield during fertility preservation for breast cancer: the TAmoxifen or Letrozole in Estrogen Sensitive tumors (TALES) randomized clinical trial	J Assist Reprod Genet	Tamoxifen	Breast	2021	Randomized trial	Not assessed
Triptorelin for Fertility Preservation in Adolescents Treated With Chemotherapy for Cancer	J Pediatr Hematol Oncol	GnRH agonist	Other	2018	Retrospective observational	Single
Fertility status of Hodgkin lymphoma patients treated with chemotherapy and adjuvant gonadotropin-releasing hormone analogues	J Assist Reprod Genet	GnRH agonist	Lymphoma/ leukemia	2015	Prospective observational	Single
Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy	Hum Reprod	GnRH agonist	Lymphoma/ leukemia	1996	Prospective observational	Yes
Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomized trial	J Clin Oncol	GnRH agonist	Lymphoma/ leukemia	2013	Randomized trial	No

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TABLE A2. Individual Studies Assessing Question of How Effective Fertoprotective Therapy Is (continued)

Title	Journal	Therapy	Cancer	Year	Study Design	Difference Between Groups (POF)
Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast CancerA Randomized Trial	JAMA	GnRH agonist	Breast	2011	Randomized trial	Yes
Goserelin with chemotherapy to preserve ovarian function in pre-menopausal women with early breast cancer: Menstruation and pregnancy outcomes	Ann Oncol	GnRH agonist	Breast	2013	Retrospective observational	Single
Gonadotropin releasing hormone agonist may minimize premature ovarian failure in young women undergoing autologous stem cell transplantation	Fertil Steril	GnRH agonist	Other	2013	Prospective observational	Yes
Cryopreservation, semen use and the likelihood of fatherhood in male Hodgkin lymphoma survivors: an EORTC-GELA Lymphoma Group cohort study	Hum Reprod	Cryopreservation	Lymphoma/ leukemia	2013	Prospective observational	Single
Gonadotropin-releasing hormone agonist for the preservation of ovarian function in survivors of haematopoietic stem cell transplantation for haematological diseases	BMC Women's Health volume	GnRH agonist	Hematologic cancers	2022	Retrospective observational	No
Gonadotropin-releasing hormone agonist protects ovarian function in young patients with ovarian malignancy undergoing platinum-based chemotherapy: A prospective study	Front Oncol	GnRH agonist	Ovarian malignancy	2022	Prospective observational	Yes
Fertility preservation in patients of childbearing age treated for breast cancer: A nationwide cohort study	Breast	Cryopreservation	Breast	2022	Retrospective observational	Yes
Clinical outcome of embryo cryopreservation in Japanese breast cancer patients: pregnancy rates after transfer of thawed embryos	J Assist Reprod Genet	Cryopreservation	Breast	2022	Retrospective observational	Single
Pregnancy, fertility concerns and fertility preservation procedures in a national study of French breast cancer survivors	Reprod Biomed Online	Multiple	Breast	2022	Prospective observational	Single
Long-Term Outcomes with Pharmacological Ovarian Suppression during Chemotherapy in Premenopausal Early Breast Cancer Patients	J Natl Cancer Inst	GnRH agonist	Breast	2022	Randomized trial	No

Abbreviations: GnRH, gonadotropin-releasing hormone; POF, premature ovarian failure.