Embryo banking among women diagnosed with cancer: a pilot population-based study in New York, Texas, and Illinois

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Abstract

Purpose The purpose of the present study is to estimate the proportion of women with cancer who return to use the embryos that they have banked and to compare this proportion to that of women without cancer who bank embryos.

Methods This is a cohort study of three groups of women from New York, Texas, and Illinois who used embryo banking in their first assisted reproductive technology (ART) treatment cycle: two groups with cancer (222 women without an infertility diagnosis and 48 women with an infertility diagnosis) and a control group without cancer (68 women with the infertility diagnosis of male factor only). Women were included only if their first ART cycle reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) occurred between 2004

and 2009. Cancer cases were identified from each State Cancer Registry from 5 years prior to initiation of ART treatment to 6 months post-initiation; mean follow-up after the first ART cycle was 2.0 years.

Results Women with cancer without an infertility diagnosis returned for a subsequent ART cycle at a lower rate (10.8 %) than those with an infertility diagnosis (31.3 %, $p=0.0010$) or the control group (85.3 %, $p<0.0001$). Among those who returned for a subsequent cycle, women with cancer waited a longer time to return (14.3 months without an infertility diagnosis and 8.3 months with an infertility diagnosis, $p=0.13$) compared to the control group (2.8 months, $p=0.0007$). The live birth rate among women who did not utilize embryo banking in their second cycle did not differ significantly across the three study groups, ranging from

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Capsule In this cohort study of women who used embryo banking in their first cycle of ART, women with cancer without an infertility diagnosis were either less likely to return for subsequent treatment or will waited a longer time to return than women with an infertility diagnosis or women that did not have cancer.

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25.0 and 42.9 % for women with cancer with and without an infertility diagnosis, respectively, to 36.2 % for women in the control group.

Conclusions Women with cancer without an infertility diagnosis are either less likely to return for subsequent treatment or will wait a longer time to return than women with an infertility diagnosis or those that do not have cancer. A longer-term study is necessary to assess whether these women return to use their frozen embryos after cancer treatment or are able to spontaneously conceive and if those subsequent pregnancies are adversely affected by the cancer diagnosis or therapy.

Keywords Oncofertility · Assisted reproduction · Cohort study · Cancer among women

Introduction

The preservation of fertility is an important quality-of-life issue for women diagnosed with cancer during their reproductive years. As the long-term trend in delaying childbearing continues, there is an increased likelihood of cancer diagnoses among women who still wish to have children [1, 2]. Cancer therapy can result in infertility, sterility, or even early menopause [3–5]. Cancer patients most likely to benefit from fertility preservation options initiated prior to cancer treatment are those who receive gonadotoxic therapies and/or radiation [6]. Embryo banking is a well-established method of preserving fertility for women diagnosed with cancer. Little is known, though, regarding the proportion of women who return to use the embryos that they have banked or how many women return for subsequent assisted reproductive technology (ART) cycles of treatment or conceive spontaneously. The purpose of this study was to explore this question, as part of a larger study linking ART cycles and State cancer registries (Fig. 1).

Materials and methods

Study data and oversight

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) contains comprehensive data from more than 90 % of all clinics providing ART and more than 97 % of all ART cycles in the USA (<http://www.sart.org>). Data were collected and verified by SART and reported to the Center for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). In 2004, after a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The SART CORS database is left-censored at 2004, that is, ART treatment details for women prior to 2004 are not available. SART makes deidentified clinical data available for research purposes to persons or entities who have agreed to comply with SART research guidelines. Patients undergoing ART at SART-associated clinics sign clinical consent forms that include permission to use their deidentified data for research. The data are submitted by individual clinics and verified by the practice director of each clinic. Approximately 10 % of the clinics are audited each year by the CDC and SART to validate the accuracy of the reported data [7].

Cancer registry data from New York, Illinois, and Texas were chosen for this study because they are large, ethnically diverse States that ranked nos. 1, 4, and 5 in number of ART cycles performed, respectively, in 2012 [7]. These three States maintain population-based cancer registries that consistently received Gold certification by the North American Association of Central Cancer Registries during 2004–2009, reflective of meeting the highest levels of data quality and standards of reporting (<http://www.naaccr.org/Certification/USCert2011.aspx>). Data available from the cancer registries included the International Classification of Disease for

Fig. 1 Description of the study population by cycle and outcomes

Oncology codes for cancer site, morphology, and age at diagnosis. The study was approved by the institutional review boards at Michigan State University, the University of Minnesota, the New York State Department of Health, the Texas Department of State Health Services, and the Illinois Department of Public Health and was analyzed using SAS 9.3 software (Cary, NC).

Linkage procedures

The SART CORS database is maintained by Redshift Technologies, Inc. for the Society for Assisted Reproductive Technology (SART). Cycles in the database to women who were residents of New York, Texas, or Illinois treated between January 1, 2004, and December 31, 2009, were linked by Redshift Technologies, Inc. Cycles for the same woman which occurred within one clinic were linked using the woman's birth date, first and last names, and social security number (when present). Cycles across clinics to the same woman were linked with the additional factors of partner's name and the sequence of ART outcomes. Cycles have been linked to individual women to determine outcomes over a course of treatment [8–12]. Redshift Technologies, Inc. also generated study-specific unique identifiers (for each woman and each cycle).

SART CORS data to state cancer registries

Redshift Technologies, Inc. sent a data file of women who were in the SART CORS and were residents of each State to the respective State Cancer Registries; the data file included the woman's first and last names, social security number (when present), date of birth, zip code of residence, and the unique identifiers. In order to achieve uniform results, all three States used probabilistic record linkage with Link Plus software, available through the Centers for Disease Control and Prevention (CDC)'s National Program of Cancer Registries (NCPR). Each of the three State Cancer Registries linked reported cancers for each woman in the data file (linked SART CORS/cancer files). Identifying variables (including names, dates, and social security numbers) were then removed, and the deidentified analytic file (which included the unique identifiers) was sent to the investigators.

SART CORS data to investigators

Redshift Technologies, Inc. sent the investigators a data file of the unique identifiers, woman's age, reproductive history, and ART treatment and outcome data for all ART cycles for that woman to link to the SART CORS/cancer files received from each of the three States. The SART CORS data records for each woman were ordered by date of treatment at cycle initiation, regardless of cycle type (fresh or thawed, autologous or donor). The data from each woman was then summarized into

a single record that included data from the initial ART treatment, such as patient age, as well as the total number of cycles. Using the data from each State, the earliest malignancy and its site of occurrence were identified for each woman; three malignancies that were classified as "unknown primary site" were deleted. The two files were then merged so that the final file included women with and without malignancies.

Independent and dependent variables

Independent variables included State (New York, Illinois, or Texas), year of ART treatment (2004, 2005, 2006, 2007, 2008, 2009), age at start of the first cycle of ART treatment in years (as 18–29, 30–34, 35–37, 38–40, 41–43, and 44–64), parity (0, 1, ≥ 2), infertility diagnosis (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, other factors, and unexplained), and cancer diagnosis (all cancers, endocrine, melanoma, breast, ovarian, cervical, uterine, and all female genital [cervix, uterus, other female genitalia, ovary, vagina, and vulva]). The dependent variables were age at cycle start, percent of women who returned for a second cycle, months between cycles, percent of women who had repeated embryo banking in their second cycle, and live birth rates.

Infertility diagnoses were defined for data entry to SART CORS as follows: male factor is the presence of abnormal semen parameters or function; endometriosis is the presence of any stage of endometriosis whether treated or untreated; ovulation disorders can have several differing definitions including multiple cysts affecting fertility, oligoovulation, or anovulation; diminished ovarian reserve is currently defined as high follicle-stimulating hormone or estradiol in the early follicular stage as measured on a clomiphene challenge test, or reduced ovarian volume, but could also have been defined by advanced maternal age for some earlier cycles in our cohort; tubal factor is any condition affecting the patency of the fallopian tubes; uterine factor includes any uterine abnormality. The category of other factors could have included immunologic, chromosomal, cancer, and any other conditions not listed in the previously defined categories. Unexplained is intended to be an absence of any defined male and female diagnoses.

Statistical analysis

We restricted the before-treatment period to 5 years prior to initiation of ART. Since women may have the same age at treatment and cancer onset, which is equivalent to saying that with 75 % probability, the ages do not differ by more than 6 months in either direction; when months of diagnosis and treatment were available, we defined a year to be ± 6 months. Diagnoses within 6 months of the start of ART treatment or an age difference of zero were included in the period before ART

(zero years difference); we viewed diagnoses within a period up to 6 months post-initial treatment to be most likely due to enhanced surveillance that resulted in the identification of a pre-existing condition.

We created a cohort study population by selecting women into two cancer groups and one control group. The two cancer groups included women with cancer prior to ART who utilized embryo banking in their first ART cycle, with and without an infertility diagnosis. The one control group included women without cancer who only had male factor as their infertility diagnosis (i.e., the woman did not have an infertility diagnosis associated with her) and only embryo banking in their first ART cycle. Women were only included in this study if their first ART treatment was included in the file; i.e., there was no history of previous ART cycles, and the treatment at the first cycle was only embryo banking. The reference group was ART pregnancies with male factor only as the infertility diagnosis. This reference group has been used in prior studies of ART outcomes because it suggests the absence of fertility issues for the female partner [13–17]. Mean follow-up after the first ART cycle was 2.0 years. The univariate analyses within and across study groups were compared using chi-square for categorical variables and *t* tests for continuous variables, with significance at $p < 0.05$.

Results

The cancer groups included 222 women without an infertility diagnosis and 48 women with an infertility diagnosis and 68 women in the control group. A description of the study population is shown in Table 1. Women with cancer without an infertility diagnosis were the youngest at their first ART cycle, and women with cancer and an infertility diagnosis were the oldest of the three groups. Breast cancer was the most frequent diagnosis (39.6 and 50.5 % for women with and without an infertility diagnosis, respectively); overall, the distribution of cancer diagnoses between the two cancer study groups did not differ significantly.

Women with cancer without an infertility diagnosis returned for a subsequent ART treatment at a lower rate (10.8 %) than those with an infertility diagnosis (31.3 %, $p = 0.0010$) or the control group (85.3 %, $p < 0.0001$) (Table 2). Among those who returned for subsequent treatment, women with cancer waited a longer time to return for a second ART cycle; those without an infertility diagnosis returned after 14.3 months and with an infertility diagnosis returned after 8.3 months ($p = 0.13$), compared to the control group, who returned after 2.8 months ($p = 0.0007$). Repeat embryo banking was substantially higher among women in the cancer group (46.7 % with an infertility diagnosis and 41.7 % without an infertility diagnosis) compared to women in the control group (19.0 %, $p = 0.050$) (Fig. 1).

The live birth rate among women who did not utilize embryo banking in their second cycle did not differ significantly across the three study groups, ranging from 25.0 and 42.9 % for women with cancer with and without an infertility diagnosis, respectively, to 36.2 % for women in the control group. Women in the banking control group represent the contemporary freeze-all embryo situation, with no attempt at pregnancy [18, 19], a high return rate for the second cycle (85.3 %), short interval between first and second cycles (2.8 months), low repeat banking rate (19.0 %), and a good live birth rate (36.2 %).

Discussion

Oncofertility is the field that has evolved over the past decade that includes “an integrated network of clinical resources that focus on developing methods to spare or restore reproductive function in patients diagnosed with cancer” [20]. In the USA, the Oncofertility Consortium was developed as a nationwide resource combining oncology and reproductive medicine, founded to address the fertility needs of young people who have been diagnosed with cancer [20]. There is an increased availability and effectiveness of contemporary fertility preservation options [21]. Prior studies have shown that age, partnership, and financial status all factor into the choice for fertility preservation measures among women with cancer [22]. Sperm and embryo banking and, more recently, oocyte banking are the established methods available to preserve fertility, although alternative methods are in development, including ovarian tissue cryopreservation and ovarian suppression with luteinizing hormone-releasing hormone analogs during chemotherapy [21, 23, 24]. Cancer therapies have been shown to negatively affect measures of ovarian reserve, including significantly lower levels of anti-Müllerian hormone, antral follicle count, follicle-stimulating hormone, and ovarian volume [25–27]. Despite a greater likelihood of impaired measures of ovarian reserve, research has shown that cancer survivors have comparable oocyte and embryo yields, as well as pregnancy rates compared to controls [17, 27, 28].

The analyses in this paper indicate that women with cancer without an infertility diagnosis who utilize embryo banking are less likely to return for subsequent cycles and do so after longer periods compared to women without cancer. Other studies have also reported low return rates among women with cancer who utilized embryo banking, ranging from 6.5 % (2005–2012, New York, NY, USA) [22], 13 % (1996–2011, Scotland) [29], 16.7 % (1997–2014, Belgium) [30], 22.5 % (1999–2011, France) [31], 26.3 % (2001–2007, Boston, USA) [17], to 33.3 % (1997–2014, Boston, USA) [32]. The two cancer groups differed on their return rates for a second cycle of treatment, months between cycles, and live birth rates but had similar rates of repeat embryo banking in their second

Table 1 Description of study population

		Cancer groups		Control
		Banking only	Banking and infertility	Banking male factor only
	<i>N</i> , women	222	48	68
Age (mean years, SD)		32.1 ± 5.4	34.4 ± 5.8	32.2 ± 4.2
Age at first cycle (%)	18–29	31.1	18.8	29.4
	30–34	32.4	20.8	45.6
	35–37	19.4	33.3	11.8
	38–40	12.6	14.6	8.8
	41–43	3.2	6.3	4.4
	≥44	1.4	6.3	0.0
	<i>P</i> values	Reference	0.014	0.84
Gravidity (%)	0	76.1	83.3	69.1
	1	12.6	10.4	20.6
	≥2	11.3	6.3	10.3
	<i>P</i> values	Reference	0.50	0.26
Infertility diagnosis (%)	Male factor	–	16.7	100
	Endometriosis	–	0.0	–
	Ovulation disorders	–	4.2	–
	Diminished ovarian res.	–	12.5	–
	Tubal factors	–	12.5	–
	Uterine factors	–	12.5	–
	Other factors	100	20.8	–
	Unexplained	–	27.1	–
Cancer diagnosis (%)	Bones and joints	0.9	0.0	–
	Brain and CNS	1.8	0.0	–
	Breast	50.5	39.6	–
	Digestive	9.0	4.2	–
	Endocrine	0.5	0.0	–
	Eye and orbit	0.0	0.0	–
	Female genitalia	10.4	29.2	–
	Leukemia	5.4	4.2	–
	Lymphoma	18.5	20.8	–
	Oral cavity and pharynx	0.5	0.0	–
	Respiratory system	1.4	0.0	–
	Skin	0.0	0.0	–
	Soft tissue, incl. heart	1.4	2.1	–
	Urinary	0.0	0.0	–
	<i>P</i> values	Reference	0.13	–
Cancer diagnosis	Cervix uteri	5.0	6.3	–
Within female genital (%)	Corpus and uterus	3.6	18.8	–
	Other female genital	0.0	0.0	–
	Ovary	1.8	4.2	–
	Vulva	0.0	0.0	–

cycle. Women who had an infertility diagnosis, in addition to cancer, were more likely to return for a second cycle (31.3 %) compared to women who only had cancer (10.8 %, $p=0.0010$) and after a shorter time period (8.3 versus 14.3 months, NS); these women also had a lower live birth

rate (25.0 versus 42.9 %, NS). These differences most likely reflect the additional influence of an infertility diagnosis on the choice, timing, and outcome of ART treatments. A longer-term study is necessary to identify whether the women with cancer wait a longer time but still return for subsequent

Table 2 Women who returned for a second cycle

		Cancer groups		Control
		Banking only	Banking and infertility	Banking male factor only
Women with first cycle	<i>N</i> , women	222	48	68
Women with second cycle	<i>N</i> , women	24	15	58
	(%)	10.8	31.3	85.3
	<i>P</i> values	Reference	0.0010	<0.0001
Age at second cycle (mean years, SD)		34.1 ± 4.4	35.6 ± 4.2	32.4 ± 4.2
Age at second cycle (%)	18–29	12.5	0.0	29.3
	30–34	41.7	53.3	43.1
	35–37	20.8	6.7	10.3
	38–40	20.8	26.7	13.8
	41–43	4.2	6.7	3.4
	≥44	0.0	6.7	0.0
	<i>P</i> values	Reference	0.29	0.13
	Months between cycles (SD)	14.3 ± 14.4	8.3 ± 9.6	2.8 ± 3.3
	<i>P</i> values	Reference	0.13	0.0007
Repeat embryo banking	(%)	41.7	46.7	19.0
	<i>P</i> values	Reference	1.0	0.050
Women without embryo banking	<i>N</i> , women	14	8	47
Used thawed embryos	(%)	100	75.0	89.4
Live birth rate	(%)	42.9	25.0	36.2
	<i>P</i> values	Reference	0.65	0.76

treatment or if they conceive spontaneously. In our study, women with cancer and an infertility diagnosis were intermediate to these two groups (women with cancer who did embryo banking and control women being treated for infertility who did embryo banking) in terms of rate of return for subsequent treatment; this delay may be due to the immediate effect of cancer treatment.

Studies have shown that a substantial proportion of women with cancer desire a future pregnancy [33–35]. In a Dutch study of women who had cryopreserved oocytes for medical reasons, with follow-up at an average of 25.3 months, none of the women had used their cryopreserved oocytes, although 23.5 % had tried to conceive [35]. More than 70 % of the women in this study intended to conceive with their cryopreserved oocytes only as a last resource option. Spontaneous conception after cancer therapy has been reported in several studies, ranging from 7.7 % [29, 31] to 13.2 % [17], although little is known about the health of these children and if they experienced a higher rate of birth defects and/or childhood cancer as a consequence of the potential gonadotoxic effect of cancer treatment [36].

In this study, the groups do not differ significantly in their live birth rates. The live birth rate with embryos banked in cancer patients without infertility was comparable to the rates in the control group, suggesting that cancer did not negatively affect embryo quality or implantation. However, the number

of women per group is small, and therefore, this result must be confirmed by a much larger study. It is unlikely that cancer has a direct effect on oocytes, but chemotherapy can adversely affect maturing follicles and radiation can have damaging effects on the ovaries, uterus, and hypothalamic-pituitary axis, with resultant increased risks for fetal growth restriction, prematurity, placental complications (including placenta accrete), and pregnancy loss [37].

The current recommendation for women with cancer is to wait at least 2 years after completing cancer therapy before attempting conception, primarily to deter women who may develop early recurrence and to allow completion of adjuvant therapies. The primary concern with a subsequent pregnancy after cancer is the potential that dormant micrometastases will be stimulated by gestational hormones. In an analysis of women diagnosed with breast cancer between 1982 and 2003 in Western Australia, Ives et al. [33] reported improved survival in women who waited at least 24 months to conceive (hazard ratio, 0.48, 95 % CI 0.27–0.83) and a non-significant protective effect for women who waited at least 6 months to become pregnant. One of the limitations of our study is the short period of follow-up (2.0 years), which may not have been sufficient to accurately assess utilization of cryopreserved embryos in the context of these recommendations. A longer-term study will be needed and is planned. Several recent meta-analyses have concluded that pregnancy after breast cancer does not

jeopardize long-term prognosis and might even confer a significant survival benefit [38–40].

In summary, women with cancer who utilize embryo banking are less likely to return for subsequent cycles and do so after longer periods compared to women without cancer. More research is needed to evaluate the effects of pregnancy after cancer on live birth rates, perinatal outcomes, and maternal and child health.

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Compliance with ethical standards

Conflict of interest The views expressed in this paper are those of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health

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