Title

Conception after chemotherapy: post-chemotherapy method of conception and pregnancy outcomes in breast cancer patients

Journal

Journal of Assisted Reproduction and Genetics, 38(7)

ISSN

1058-0468

Authors

Abel, Mary Kathryn
Wald, Kaitlyn
Sinha, Nikita
et al.

Publication Date

2021-07-01

DOI

10.1007/s10815-021-02133-0

Peer reviewed

Journal of Assisted Reproduction and Genetics (2021) 38:1755–1765
https://doi.org/10.1007/s10815-021-02133-0

FERTILITY PRESERVATION

Conception after chemotherapy: post-chemotherapy method of conception and pregnancy outcomes in breast cancer patients

Mary Kathryn Abel[1,2] · Kaitlyn Wald[2] · Nikita Sinha[2,3] · Joseph M. Letourneau[2,4] · Rhodel Simbulan[2] · Evelyn Mok-Lin[2] · Marcelle I. Cedars[2] · Mitchell P. Rosen[2]

Received: 10 September 2020 / Accepted: 25 February 2021 / Published online: 19 March 2021

Abstract

Purpose As the paradigm shifts towards improving cancer survivorship, an important concern for reproductive-aged women diagnosed with cancer is how their disease and its treatment will affect their future fertility. We sought to characterize pregnancy attempts and outcomes in breast cancer patients following chemotherapy.

Methods We conducted a prospective cohort study of women diagnosed with breast cancer seen between 2010 and 2019. A questionnaire was administered following cancer treatment with questions regarding oncologic and reproductive history and attempts and method of conception.

Results Of 181 participants, 46 (25.4%) attempted to conceive following chemotherapy. Thirty-five patients (76.1%) had return of ovarian function. Of those, 34 patients (mean age 32.8 years) first attempted to conceive by intercourse, and 22 (64.7%) became pregnant, resulting in 17 live births. Of the remaining 12 who did not successfully conceive through intercourse, eight went on to try other methods, resulting in five additional pregnancies and one live birth. Twelve patients (mean age 34.6 years) proceeded directly to ART; of those, eight (66.7%) became pregnant, resulting in six live births.

Conclusion In breast cancer patients with return of ovarian function after chemotherapy, half were able to conceive by intercourse alone. In order to maximize reproductive potential in patients who have return of ovarian function, providers should offer natural conception as a reasonable option prior to the use of cryopreserved tissue. For those who did not attempt to conceive on their own, the use of pre-treatment cryopreserved eggs or embryos had a high likelihood of success.

Keywords Fertility preservation · Breast cancer · Chemotherapy · Pregnancy outcomes

Introduction

The advancement of anti-cancer agents in the treatment of breast cancer has significantly improved long-term outcomes for patients. As such, a growing concern for the nearly 13,000 women of reproductive age diagnosed with breast cancer in the USA each year is how the disease and its treatment will impact their future fertility [1]. While several studies have documented the gonadotoxic effect of chemotherapy agents, 27-75% of reproductive-aged women treated with chemotherapy will regain ovarian function after treatment [2–5]. The return of menses, however, does not guarantee the ability to conceive, and there still remains an increased risk of early menopause despite resumption of menses, further limiting the reproductive potential of this population [6–8].

In young cancer patients who are remote from desiring conception, it is difficult to perform clinical trials that quantify the impact of chemotherapy agents on pregnancy rates for these patients given the long period of follow-up time required. In the Childhood Cancer Survivor Study cohort, pregnancy rates were not strongly associated with chemotherapy exposure, except at very high cumulative doses [9]. Newer studies have shown cancer survivors are approximately 38%

✉ Mary Kathryn Abel
marykathryn.abel@ucsf.edu

1 University of California, San Francisco School of Medicine, San Francisco, CA, USA

2 Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, 499 Illinois Street, 6th Floor, San Francisco, CA 94158, USA

3 Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

4 Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, USA

less likely to achieve pregnancy after their diagnosis compared to the general population [10, 11].

Due to this compromise in fertility, fertility preservation should be discussed with patients prior to the initiation of cancer therapy [12, 13]. Because this practice is relatively new, limited data are available that evaluate the success of post-chemotherapy conception and/or use of cryopreserved eggs and embryos. Moreover, while research does suggest that pregnancy after breast cancer is safe, available studies have used a retrospective approach due to the nature of the research question [14–21].

We sought to prospectively characterize pregnancy attempts, method of conception, and pregnancy outcomes in a cohort of young breast cancer patients treated with chemotherapy. This information can aid in the counseling of young breast cancer patients undergoing consultation for pretreatment fertility preservation and reproductive age breast cancer survivors desiring pregnancy following chemotherapy.

Methods

Study population

We performed a prospective cohort study from 2010 to 2019. Patients diagnosed with breast cancer who presented to the University of California, San Francisco Center for Reproductive Health (UCSF CRH) for fertility preservation during the study time period were longitudinally surveyed about their cancer treatment, history, and reproductive attempts. Women were included in the study if they were ages 18-45 years at the time of enrollment, diagnosed with breast cancer, and received chemotherapy for their breast cancer treatment. Patients were excluded if they had received any pelvic radiation treatment prior to enrollment or had a history of hysterectomy or oophorectomy.

Survey and study visits

A questionnaire was developed to query reproductive history after cancer treatment. The survey included information about demographics, medical history, gynecological history, and obstetrical history. The survey was piloted on 10 patients and edited for ease of use and readability before being distributed to the entire study population. At the initial fertility preservation evaluation, patients went through a structured interview including detailed information about their new cancer diagnosis, past medical history, and obstetrical history. At post-treatment visits, additional information regarding the patient's cancer therapy was obtained and cross-validated with medical records. Menstrual history and use of tamoxifen, aromatase inhibitors, and gonadotropin-releasing hormone (GnRH) agonists were recorded at each post-treatment visit. The end of systemic, gonadotoxic chemotherapy was determined through the questionnaire and interviews at medical visits.

Assessment of ovarian reserve

Ovarian reserve was assessed by measuring antral follicle count (AFC) at the initial fertility preservation consultation. Transvaginal ultrasound was performed on the GE VolusonS8 machine by the same two experienced clinicians. Follicles measuring between 2 and 10 mm in both ovaries were counted in the AFC, consistent with the international standard measurement [22]. All patients were offered follow-up AFC measurements starting 3 months after completion of chemotherapy for assessment of recovery of ovarian reserve, unless they were on ovarian suppression. In our cohort of patients attempting to conceive through intercourse, 15 patients presented for AFC evaluation and counseling just prior to attempting conception. If patients were found to be in menopause, they were encouraged to proceed directly to assisted reproductive technology (ART) using previously preserved eggs/embryos or to utilize an egg donor.

Statistical analysis

Electronic medical record data were extracted and de-identified. Statistical analyses were performed using Stata version 14.2 (Stata Corp, College Station, TX). Statistical significance was defined by two-sided p-values <0.05. Descriptive statistics were used to demonstrate the characteristics of patients trying to conceive. T-tests and chi-square tests were used, as appropriate, to compare data among survey responders who did and did not attempt to conceive, individuals who attempted conception with intercourse compared to those who used ART, and pregnant and non-pregnant individuals who attempted to conceive through intercourse alone.

Ethical approval

All study procedures were reviewed and approved by the University of California, San Francisco Committee on Human Research. Informed consent was obtained from all individual participants included in the study, and all participants gave written consent to use de-identified information for research purposes and publications.

Results

Patient characteristics

A total of 296 breast cancer patients seen at our center during the study timeframe were approached. Seventy-two patients declined (24.3%); of those remaining, 43 patients were

excluded because they did not receive chemotherapy, leaving 181 patients who were eligible to complete the post-treatment surveys. A total of 157 patients (86.7%) completed at least one post-treatment survey, and 40 of these individuals attempted to conceive (Fig. 1). The characteristics of the 157 individuals who completed the survey were compared (Table 1). Patients who did not attempt to conceive were more likely to have estrogen receptor (ER) positive disease (81.2% vs. 62.5%, $p = 0.016$). Patients who attempted to conceive, on the other hand, were more likely to have ER negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative disease (30.0% vs. 10.6%, $p = 0.004$). No other demographic and clinical characteristics were significantly different between these two groups. An additional 24 patients (13.3%) did not complete a post-treatment survey but underwent chart review; of these patients, six attempted to conceive (Fig. 1). There were no statistically significant differences between the participants who attempted to conceive and completed the survey ($n = 40$) and those who attempted to conceive and underwent chart review ($n = 6$).

Baseline demographics of all 46 individuals who attempted to conceive are presented in Table 2. Patients were on average 33 ± 4.5 years old when they were diagnosed with cancer and waited an average of 3.7 ± 2.1 years between date of diagnosis and date of first attempt at conception. The majority of patients made initial contact with the UCSF CRH quickly following their diagnosis, with an average of 23 days from date of cancer diagnosis. Six out of 46 patients (13.3%) were BRCA positive. A total of 26 patients were initially diagnosed with estrogen receptor positive (ER+) breast cancers, and 35 patients received cyclophosphamide as part of their chemotherapy regimen. Average pre-chemotherapy AFC was 11 with a standard deviation of 8 (range: 0-39). Other than return of menses, there were no differences in patient characteristics prior to chemotherapy treatment, cyclophosphamide or GnRH agonist use, or age at first attempt at conception between individuals who attempted to conceive through intercourse compared to those who attempted to conceive through ART. The only difference was length of attempt of conception (6.7 months for intercourse vs. 1.3 months for ART, $p < 0.001$).

Of the 46 patients who attempted to conceive, 33 of them underwent pre-treatment cryopreservation, with a total of 8 freezing eggs (24.2%), 20 freezing embryos (60.6%), 4 freezing a combination of eggs and embryos (12.1%), and 1 unknown because she ultimately elected cryopreservation at a different facility and the records were not available. The average number of eggs frozen per patient was 16 (range: 2-32), while the average number of embryos frozen per patient was 9 (range: 1-21). When comparing individuals who attempted to conceive through intercourse vs. ART, there was no statistically significant difference between number of eggs (14 vs. 21, $p = 0.624$) and number of embryos (8 vs. 9, $p = 0.174$) frozen.

Table 1 Patient demographics comparing breast cancer patients who attempted to conceive ($n = 40$) and patients who did not attempt to conceive and completed survey ($n = 117$)

Characteristics	Overall ($n = 157$)	Attempted to conceive ($n = 40$)	Did not attempt to conceive ($n = 117$)	p-value
Age at diagnosis in years, mean (SD[1]) ($n = 148$)	35 (5.0)	33 (4.4)	35 (5.0)	$p = 0.353$
Nulliparous	102 (65.0)	25 (62.5)	77 (65.8)	$p = 0.705$
Hormone receptor[2]				
ER+	120 (76.4)	25 (62.5)	95 (81.2)	$p = 0.016$*
HER2+ ($n = 152$)	59 (38.8)	11 (28.2)	48 (42.5)	$p = 0.115$
ER-PR-HER2- ($n = 153$)	24 (15.7)	12 (30.0)	12 (10.6)	$p = 0.004$*
BRCA[3] positive ($n = 142$)	16 (11.3)	5 (13.5)	11 (10.5)	$p = 0.615$
Pre-chemo AFC[4], median (range) ($n = 156$)	13 (0-54)	11 (0-39)	13 (0-54)	$p = 0.275$
Cyclophosphamide use	111 (70.7)	33 (82.5)	78 (66.7)	$p = 0.058$
GnRH[5] agonist use during chemotherapy ($n = 156$)	69 (44.2)	20 (50.0)	49 (42.2)	$p = 0.394$

Data are expressed as n (%) unless otherwise specified

Total $n = 157$ unless otherwise specified

[1] *SD* standard deviation

[2] *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[3] *BRCA* breast cancer gene

[4] *AFC* antral follicle count

[5] *GnRH* gonadotropin-releasing hormone

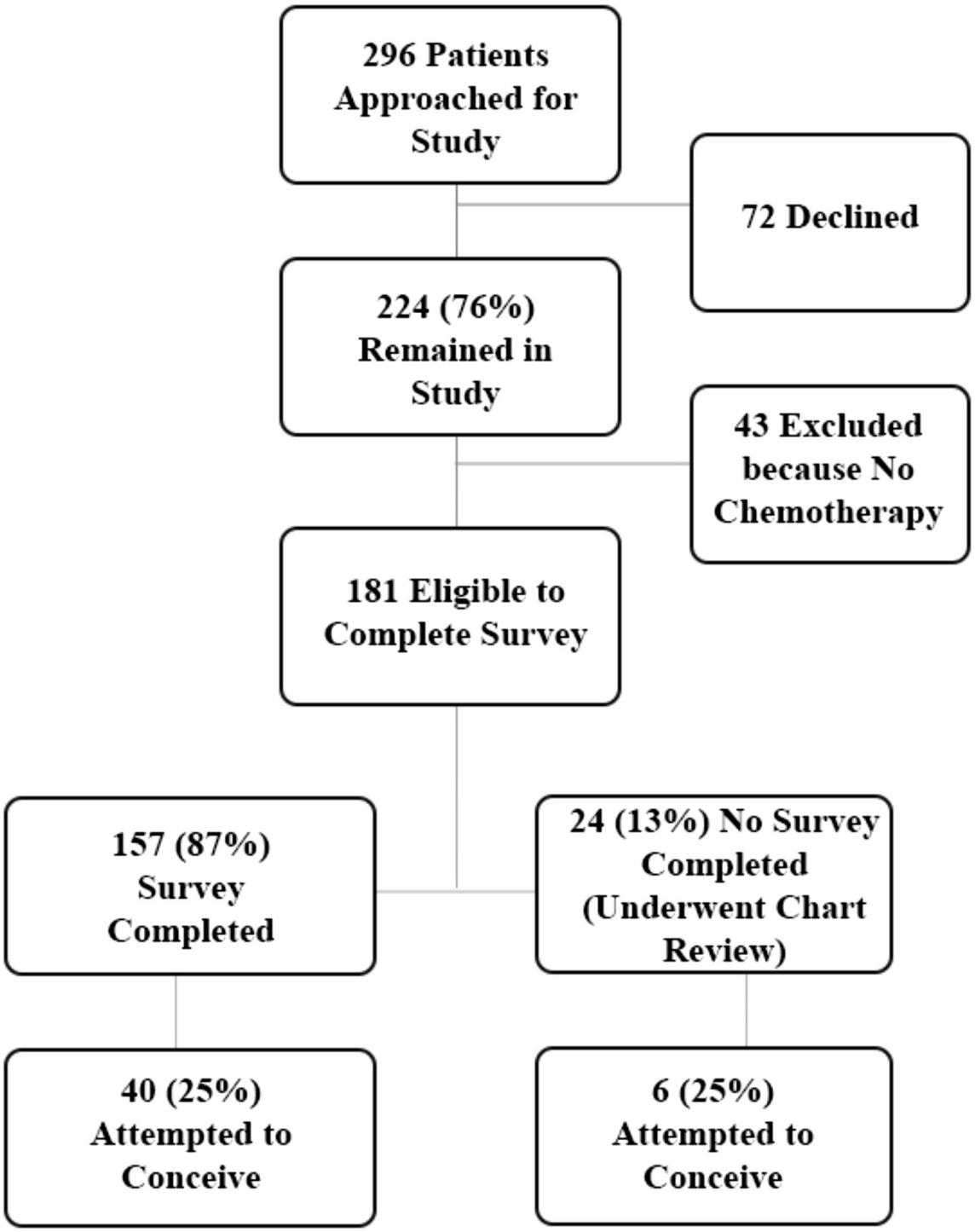

Fig. 1 Flowchart of sample population

Pregnancy attempts and outcomes by intercourse after chemotherapy

The details of the conception methods used by the 46 patients who attempted to conceive after chemotherapy are detailed in Fig. 2. Thirty-four individuals (73.9%) initially attempted to conceive through intercourse. Of these patients, 22 patients (64.7%) successfully became pregnant. Table 3 compares the baseline characteristics between the pregnant and not pregnant patients in this group. There were no significant differences in age, parity, hormonal receptor status, use of cyclophosphamide, use of GnRH agonists during chemotherapy, and time after chemotherapy treatment prior to conception attempts. Those who became pregnant attempted to conceive

Table 2 Patient demographics of 46 breast cancer patients attempting to conceive through intercourse or ART

Characteristics	Overall (n = 46)	Intercourse (n = 34)	ART (n = 12)	p-value
Age at diagnosis (years), mean (SD[1]) (n = 45)	33 (4.5)	32.8 (3.9)	34.6 (5.9)	0.074
Age at first conception attempt in years, mean (SD) (n = 45)	37 (4.1)	37.3 (3.6)	39.2 (5.0)	0.180
Nulliparous	28 (60.1)	22 (64.7)	6 (50.0)	0.370
Hormone receptor[2]				
ER+ (n = 44)	26 (59.1)	22 (66.7)	4 (36.4)	0.077
HER2+ (n = 43)	12 (27.9)	9 (28.1)	3 (27.3)	0.957
ER-PR-HER2- (n = 44)	15 (34.1)	9 (27.3)	6 (54.6)	0.098
BRCA[3] positive (n = 45)	6 (13.3)	4 (12.1)	2 (16.7)	0.649
Pre-chemo AFC[4], median (IQR[5]) (n = 45)	10 (5-15)	11 (5-14)	9 (7-19)	0.740
Cyclophosphamide use (n = 43)	35 (81.4)	27 (84.4)	8 (72.7)	0.392
GnRH[6] agonist use during chemotherapy (n = 44)	23 (50.0)	17 (50.0)	6 (50.0)	0.723
Time between attempt and chemotherapy end (years), median (IQR)	3.2 (2.1-5.1)	3.2 (2.1-5.1)	3.3 (2.3-5.0)	0.143
Length of attempt (months), median (IQR) (n = 44)	3 (1-8)	4 (2-9)	1 (1-1)	< 0.001*
Number of pre-treatment eggs frozen per cycle, mean (range) (n = 12)	16 (2-32)	14 (2-23)	21 (14-32)	0.624
Number of pre-treatment embryos frozen per cycle, mean (range) (n = 24)	9 (1-21)	8 (3-19)	9 (1-21)	0.174

Data are expressed as n (%) unless otherwise specified

Total n = 46 unless otherwise specified

[1] *SD* standard deviation

[2] *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[3] *BRCA* breast cancer gene

[4] *AFC* antral follicle count

[5] *IQR* interquartile range

[6] *GnRH* gonadotropin-releasing hormone

for an average of 4 months while those who did not attempted on average for 10 months (p = 0.58). Pre-chemotherapy average AFC was 10 in patients who became pregnant and 14 in those who did not become pregnant (p = 0.82). The AFC at time of first attempt was 4 (range: 1-10) in those who became pregnant, while the AFC in those who did not become pregnant was 6 (range: 0-14, p = 0.4). Only seven patients (31.8%) who became pregnant and eight patients (66.7%) who did not become pregnant had recorded AFCs at the onset of conception attempts.

Of the 22 patients who became pregnant through intercourse, 17 (77.3%) of these pregnancies resulted in a live birth (Table 4). The average gestational age at delivery was 39 weeks (SD 2.8 weeks), with one baby born at 29 weeks in the setting of IUGR. The average birth weight was 3168 g (SD 807 g). Three pregnancies were complicated by 1) severe intrauterine growth restriction (IUGR), 2) gestational diabetes mellitus (DM), and 3) gestational hypertension. Five patients had miscarriages, with an average gestational age at time of diagnosis of 8 weeks.

Eight of the 12 patients (66.7%) who did not become pregnant through intercourse went on to use ART, with six (75.0%) undergoing IUI and two (25.0%) undergoing FET (Fig. 2, Table 4). Of the six who underwent IUI, two patients had a subsequent pregnancy, and both miscarried at an average gestational age of 9.5 weeks. An additional two patients underwent FET after failed IUI, resulting in one pregnancy and one miscarriage at 7 weeks.

Pregnancy attempts and outcomes by ART after chemotherapy

Of the 46 patients in our entire cohort, 11 (23.9%) patients underwent ART using egg donation or FET due to lack of return of ovarian function post-chemotherapy (Fig. 2), and one additional patient went directly to IUI despite having return of ovarian function, as the patient was 40 years of age and desired a more aggressive approach. Ten of the 12 patients had pre-treatment cryopreserved eggs or embryos. Of the 12 patients, eight (66.7%) became pregnant, and six pregnancies (75.0%) resulted in a live birth (Table 4). Of the six live births, four were conceived through FET and two were conceived using donor eggs in the setting of no pre-treatment cryopreservation. The average gestational age at delivery was 38

Table 3 Pregnant vs. not pregnant by intercourse after chemotherapy

	Pregnant (n = 22)	Not pregnant (n = 12)	p-value
Age at diagnosis (years), mean (SD[1]) (n = 33)	32 (3.5)	34 (4.4)	0.36
Age at first conception attempt (years), mean (SD) (n = 33)	36 (3.0)	39 (4.1)	0.22
Nulliparous	13 (59.0)	9 (75.0)	0.35
Hormone receptor[2]			
ER+ (n = 33)	13 (59.1)	9 (75.0)	0.17
HER2+ (n = 32)	7 (31.8)	2 (16.7)	0.11
ER-PR-HER2- (n = 33)	8 (36.4)	1 (8.3)	0.10
Pre-chemo AFC[3], median (IQR[4])	10 (5-16)	12 (6-16)	0.86
Cyclophosphamide use (n = 32)	19 (86)	8 (67)	0.13
GnRH[5] agonist use during chemotherapy (n = 33)	11 (50.0)	6 (50.0)	0.38
Time between first attempt and end of chemo (years), median (IQR)	3.1 (1.5-5.1)	3.5 (2.8-4.7)	0.65
AFC[3] at attempt, median (IQR) (n = 15)	3 (2-7)	5 (2-9)	0.40
Length of attempt (months) median (IQR) (n = 33)	3 (1-4)	8 (6-12)	0.58

Data are expressed as n (%) unless otherwise specified

Total n = 34 unless otherwise specified

[1] *SD* standard deviation

[2] *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[3] *AFC* antral follicle count

[4] *IQR* interquartile range

[5] *GnRH* gonadotropin-releasing hormone

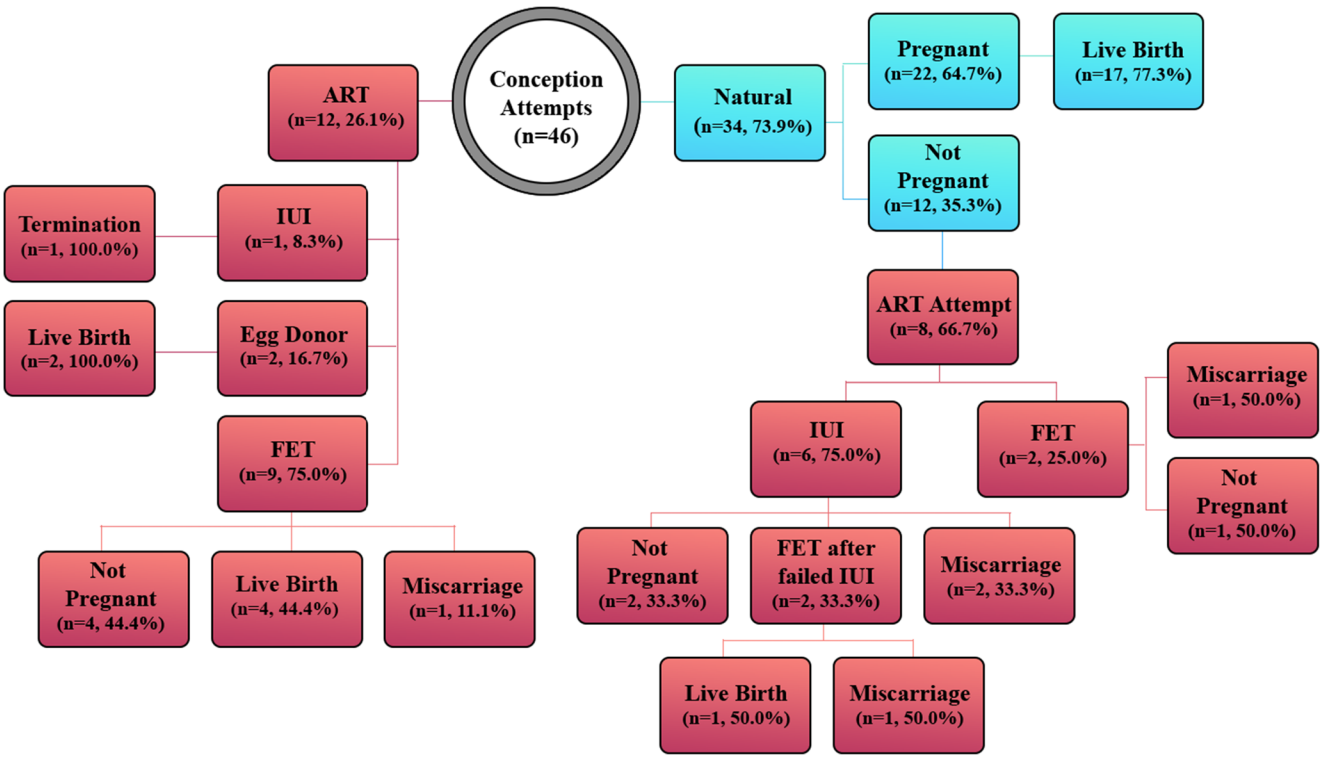

Fig. 2 Flowchart of pregnancy attempts for our cohort of patients who attempted to conceive through intercourse (right) or assisted reproductive technology (left). ART = assisted reproductive technology, IUI = intrauterine insemination, FET = frozen embryo transfer

Table 4 Pregnancy outcome for 32 pregnant patients who successfully conceived

Pregnancy method	Result of pregnancy	Birth weight (g)	Complications
IC[1] alone	Delivery at 41 wks	2855	None
IC alone	Delivery at 41 wks	3884	None
IC alone	Delivery at 41 wks	3232	None
IC alone	Delivery at 41 wks	3671	Gestational HTN[2]
IC alone	Delivery at 40 wks	3827	None
IC alone	Delivery at 40 wks	3033	None
IC alone	Delivery at 40 wks	4224	None
IC alone	Delivery at 40 wks	3175	None
IC alone	Delivery at 40 wks	3147	None
IC alone	Delivery at 40 wks	3430	None
IC alone	Delivery at 40 wks	2730	None
IC alone	Delivery at 39 wks	3402	None
IC alone	Delivery at 39 wks	2721	None
IC alone	Delivery at 39 wks	3600	None
IC alone	Delivery at 29 wks	595	Severe IUGR[3]
IC alone	Delivery at unknown gestation	Unknown	Unknown
IC alone	Delivery at unknown gestation	Unknown	Gestational DM[4]
IC alone	Miscarriage at 9 wks		
IC alone	Miscarriage at 8 wks		
IC alone	Miscarriage at 6 wks		
IC alone	Miscarriage at unknown gestation		
IC alone	Miscarriage at unknown gestation		
IC ➔ IUI[5]	Miscarriage at 9.5 wks		
IC ➔ IUI	Miscarriage at unknown gestation		
IC ➔ IUI ➔ FET	Delivery at 39 wks	3410	None
IC ➔ IUI ➔ FET	Miscarriage at 7 weeks		
IC ➔ FET[6]	Miscarriage at 7 weeks		
IUI alone	Surgical termination at 21 wks for fetal anomalies		
FET alone	Delivery at unknown gestation	Unknown	Unknown
FET alone	Delivery at 38 wks	2438, 2807	C-section for twin delivery
FET alone	Delivery at 36 wks	2849	Velamentous cord insertion, pre-eclampsia
FET alone	Delivery at 36 wks	1891, 2135	C-section for twin delivery, superimposed pre-eclampsia, severe IUGR, gestational DM
FET alone	Miscarriage at 7 wks		
Egg donor alone	Delivery at 40 wks	3033	None
Egg donor ➔ egg donor	Delivery at 40 wks	2820	None

[1] *IC* intercourse

[2] *HTN* hypertension

[3] *IUGR* intrauterine growth restriction

[4] *DM* diabetes mellitus

[5] *IUI* intrauterine insemination

[6] *FET* frozen embryo transfer

weeks (SD 2 weeks). Two of the six patients underwent cesarean section for twin pregnancies. After excluding these twin pregnancies, the average birth weight was 2900 g (SD 94 g). Two pregnancies were complicated by 1) pre-eclampsia, and 2) superimposed pre-eclampsia, severe IUGR, and gestational diabetes mellitus. Of the two patients who conceived with ART on the first attempt but did not have

a live birth, one underwent surgical termination at 21 weeks due to fetal anomalies, and one had a miscarriage at 7 weeks.

Interruption of hormonal treatment

Of the 46 patients attempting to conceive, 26 of them had ER+ disease, and 25 of these patients were treated with either Tamoxifen or an aromatase inhibitor for hormone suppression post-chemotherapy. Of these patients, 19 patients (73.1%) interrupted hormonal treatment in order to conceive. A total of 16 patients attempted to conceive through intercourse, and eight out of 16 patients (50.0%) became pregnant. The three remaining patients who interrupted hormonal therapy attempted to conceive with ART, and two out of three (66.7%) became pregnant through FET.

Recurrence

Recurrence of primary breast cancer has occurred in only one of the 46 patients who attempted conception (2.2%). This patient had hormone receptor positive disease and declined treatment with hormonal therapy. She spontaneously conceived through intercourse and delivered without complications, 3 years after treatment for breast cancer. Her cancer recurred with bone metastases 17 months following her delivery.

Discussion

It is well known that individuals who undergo cancer treatment are more likely to experience a shortened reproductive window [6]. In our clinical practice, like many others, the approach has been to attempt natural conception after treatment if possible; however, there are limited data to substantiate this practice. To answer this question, we sought to prospectively characterize pregnancy attempts, method of conception, and pregnancy outcomes in our cohort of breast cancer patients treated with chemotherapy. Overall, we found that nearly three-quarters of patients attempted conception with intercourse following chemotherapy, with half of these patients having a live birth without any additional reproductive technology. This pregnancy rate was comparable to that of individuals in our cohort who attempted to conceive through ART initially rather than intercourse. These data suggest that in order to maximize reproductive potential in patients who have return of ovarian function, natural conception should be attempted first, even in patients with limited ovarian reserve, prior to using alternative methods like ART. This approach allows patients who have cryopreserved eggs or embryos and are able to conceive naturally initially to utilize this tissue later in their reproductive life if they desire to further grow their family or are unsuccessful with attempts at natural conception.

Of the 181 eligible individuals who participated in our study, only 46 attempted to become pregnant following chemotherapy during the study period, which is consistent with prior literature [23]. Compared to those who attempted to conceive, those who did not were significantly more likely to have ER positive disease. Potential reasons for this difference include fear of breast cancer recurrence, concern for halting hormone therapy during pregnancy, advanced age at the time of completing 5-10 years of hormone therapy, or physician concerns about the safety of pregnancy in women with a history of ER positive disease [24]. While current research suggests pregnancy after breast cancer does not increase a woman's risk of recurrence, this research has been limited by retrospective analysis and limited follow-up time [25]. The relationship between halting hormone therapy during pregnancy and breast cancer recurrence is similarly unclear, with new clinical trials, including the Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) trial, aiming to answer this question [26]. The findings of this study will be critical, as we anticipate the number of individuals attempting to conceive following chemotherapy will only rise as fertility preservation counseling becomes more widely available and survival improves.

Although intercourse works well in this population, the benefits of fertility preservation are significant. Other than return of menses, there were no significant differences between individuals who attempted to conceive through intercourse and those who attempted to conceive using ART for nearly all variables measured. Therefore, there were no markers that identified women who would require ART for family building. Further, the only meaningful difference between the two populations was length of attempt of conception, where individuals who attempted to conceive through intercourse spent on average 6.7 months trying to conceive compared to 1.3 months when using ART, despite similar pregnancy outcomes. As such, individuals who desire decreased time to conception, like those who are hormone receptor positive and would like to limit their hormone therapy break, may benefit from utilizing ART as a means for conception.

We also found no significant predictors of successful conception for individuals attempting to conceive through intercourse after chemotherapy, including age at conception and pre-chemotherapy AFC. These results suggest the current available pre-treatment fertility and ovarian reserve markers cannot predict who may require assistance with conception following treatment. This is invaluable information for providers counseling patients about preservation options prior to chemotherapy treatment, as it emphasizes the importance of offering fertility preservation to all patients, regardless of age

or baseline fertility assessment [12, 13]. It is also valuable information for patients trying to decide if they would like to pursue fertility preservation. However, while there were no statistically significant differences between those who did and did not achieve conception through intercourse in our study, it is important to note that there may be factors like age at first conception attempt that could be clinically meaningful for providers and patients.

Overall, pregnancies that were achieved through intercourse or ART were relatively uncomplicated, with most complications occurring in the setting of twin deliveries following ART. Studies have shown that while the majority of births in women with a history of breast cancer are uncomplicated, there is an overall increased risk of delivery complications, cesarean section, very preterm birth, and low birth weight in these patients compared to controls [27, 28]. Moreover, a prospective cohort study recently showed the risk of preterm birth and pre-eclampsia in women with cancer who become pregnant with egg donors was higher than those without cancer history [29]. Our data suggests a possible increased risk in spontaneous abortion in patients who initially or eventually attempted to conceive through ART; however, limited data exist about the success and complications of ART methods following breast cancer treatment.

Over half of the patients in this study were hormone receptor positive, and 73.1% chose to halt hormone therapy with Tamoxifen or an aromatase inhibitor to conceive, with 10 individuals becoming pregnant through either intercourse or ART. The only recurrence in our cohort was a patient who had declined recommended hormonal therapy. Our study was underpowered to assess the question of recurrence in pregnancy. Previous studies have shown that there is no apparent increased risk of recurrence following pregnancy for individuals with hormone receptor positive disease [25, 30, 31]. Recommendations have increasingly shifted towards 10 years of adjuvant hormone therapy rather than 5 years, significantly shortening the fertility window for patients who are unable or unwilling to interrupt therapy [32]. More data, including that from the POSITIVE trial, are needed to understand the safety of interruption of hormone therapy for pregnancy.

There are several strengths to our study. Most notably, this is the only study to date that looks prospectively at conception attempts using intercourse and ART following pre-treatment fertility preservation counseling. As such, this research can be used to guide patients deciding about fertility preservation prior to undergoing chemotherapy, particularly regarding post-treatment conception rates with intercourse as well as the rates and use of ART. Our study is limited by a relatively small sample size of 46 patients all recruited from a single institution. Additionally, while many of the factors we believed to be most predictive for conception following chemotherapy were measured, several important factors went unmeasured. For example, AFC at the time of attempt was recorded for only 15 patients who attempted to conceive through intercourse. Anti-Mullerian hormone was not available for our patient population. We were also unable to record the exact chemotherapy regimen and dose for each participant. We lacked information regarding survival rates and the percentage of patients who were considered to be healthy enough to attempt pregnancy. Additionally, there is the potential for response bias, particularly given that a small percentage of patients underwent chart review rather than survey completion, as this has a chance of missing patients who attempted spontaneous conception unsuccessfully and never sought treatment. Despite this bias, chart review allowed us to identify more patients, including six individuals who had documented attempts at conception, and thus we felt it was important to include these patients in our results.

Conclusion

Chemotherapy for breast cancer treatment has improved long-term outcomes for patients, including young women who are of reproductive age. Appropriately, a dramatic increase in the percentage of this population undergoing fertility preservation prior to the initiation of chemotherapy has coincided with the improved survival rates. Increasingly, these patients are returning to care, desiring post-treatment conception. There are limited data to guide providers and their patients on the best approach to post-chemotherapy family building. Our findings suggest that it is reasonable to offer natural conception prior to the use of cryopreserved tissue in patients menstruating following treatment, unless these patients would prefer to use ART for other reasons like limiting time off of hormonal therapy. The duration of attempt must be individualized to each patient; however, our data suggests that a minimum of 4-6 months is reasonable. Our findings also highlight the difficulty in predicting which patients are likely to need ART for post-chemotherapy conception. To better guide providers and patients in their decision-making, additional research in a larger cohort of patients with a variety of different cancers is critical.

Acknowledgements We would like to make a special thanks to our nurses and care coordinators who provided patient education and fertility preservation coordination.

Code availability Code may be made available upon request.

Author contribution M.K.A. and K.W.'s roles included data collection, data analysis, and manuscript writing; N.S. and J.M.L.'s roles included study design and data collection; R.S.'s role included manuscript writing; E.M.L., M.I.C., and M.R.'s roles included study design and manuscript writing.

Funding This study was supported by departmental research funding within the University of California, San Francisco Department of Obstetrics, Gynecology, and Reproductive Sciences. Additionally, this project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number TL1 TR001871.

Data availability We are unable to provide our data due to its identified nature.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of California, San Francisco (UCSF) Committee on Human Research and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication As part of the consent process, all participants gave written consent to use de-identified information for research purposes and publications.

Competing interests The authors declare no competing interests.

References

1. American Cancer Society. Breast cancer facts & figures (2019-2020). Am Cancer Soc. 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breastcancer-facts-and-figures-2019-2020.pdf.2019-2020.pdf2019-2020.pdf.2019-2020.pdf.
2. Kim HA, Choi J, Park CS, Seong MK, Hong SE, Kim JS, et al. Post-chemotherapy serum anti-Müllerian hormone level predicts ovarian function recovery. Endocr Connect. 2018;7(8):949–56. https://doi.org/10.1530/EC-18-0180.
3. Yu B, Douglas N, Ferin MJ, Nakhuda GS, Crew K, Lobo RA, et al. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. Cancer. 2010:NA. https://doi.org/10.1002/cncr.25037.
4. Henry NL, Xia R, Banerjee M, Gersch C, McConnell D, Giacherio D, et al. Predictors of recovery of ovarian function during aromatase inhibitor therapy. Ann Oncol. 2013;24:2011–6. https://doi.org/10.1093/annonc/mdt149.
5. Ruddy KJ, O'Neill A, Miller KD, Schneider BP, Baker E, Sparano JA, et al. Biomarker prediction of chemotherapy-related amenorrhea in premenopausal women with breast cancer participating in E5103. Breast Cancer Res Treat. 2014;144:591–7. https://doi.org/10.1007/s10549-014-2891-0.
6. Letourneau JM, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. Cancer. 2012;118:1933–9. https://doi.org/10.1002/cncr.26403.
7. Partridge AH, Ruddy KJ, Gelber S, Schapira L, Abusief M, Meyer M, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril. 2010;94:638–44. https://doi.org/10.1016/j.fertnstert.2009.03.045.
8. Silva C, Caramelo O, Almeida-Santos T, Rama ACR. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-Analysis. Hum Reprod. 2016;31(12):2737–49. https://doi.org/10.1093/humrep/dew224.
9. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol. 2002;187(4):1070–80.
10. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, et al. The impact of cancer on subsequent chance of pregnancy: a population-based analysis. Hum Reprod. 2018;33(7):1281–90. https://doi.org/10.1093/humrep/dey216.
11. Van Dorp W, Haupt R, Anderson RA, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. J Clin Oncol. 2018;36(21):2169–80. https://doi.org/10.1200/JCO.2017.76.3441.
12. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2020;31:1664–78. https://doi.org/10.1016/j.annonc.2020.09.006.
13. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994–2001. https://doi.org/10.1200/JCO.2018.78.1914.
14. Dabrosin C. An overview of pregnancy and fertility issues in breast cancer patients. Ann Med. 2015;47(8):673–8. https://doi.org/10.3109/07853890.2015.1096953.
15. Cobo A, García-Velasco J, Domingo J, Pellicer A, Remohí J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod. 2018;33(12):1–10. https://doi.org/10.1093/humrep/dey321.
16. Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril. 2016;105:755–64. https://doi.org/10.1016/j.fertnstert.2015.11.027.
17. Porcu E, Venturoli S, Damiano G, Ciotti PM, Notarangelo L, Paradisi R, et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod BioMed Online. 2008;17(2):265–7. https://doi.org/10.1016/S1472-6483(10)60204-0.
18. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016;160(2):347–60. https://doi.org/10.1007/s10549-016-3989-3.
19. Iqbal J, Amir E, Rochon PA, Giannakeas V, Sun P, Narod SA. Association of the timing of pregnancy with survival in women with breast cancer. JAMA Oncol. 2017;3(5):659–65. https://doi.org/10.1001/jamaoncol.2017.0248.
20. Lambertini M, Martel S, Campbell C, Guillaume S, Hilbers FS, Schuehly U, et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2–positive early breast cancer: analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer. 2019;125(2):307–16. https://doi.org/10.1002/cncr.31784.
21. Lambertini M, Ameye L, Hamy AS, Zingarello A, Poorvu PD, Carrasco E, et al. Pregnancy after breast cancer in patients with germline BRCA mutations. J Clin Oncol. 2020;38:3012–23. https://doi.org/10.1200/JCO.19.02399.

22. Broekmans FJM, De Ziegler D, Howles CM, Gougeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. Fertil Steril. 2010;3:1044–51. https://doi.org/10.1016/j.fertnstert.2009.04.040.
23. Poorvu PD, Gelber SI, Zheng Y, Ruddy KJ, Tamimi RM, Peppercorn J, et al. Pregnancy after breast cancer: results from a prospective cohort of young women with breast cancer. Cancer. 2020. https://doi.org/10.1002/cncr.33342.
24. Lambertini M, Di Maio M, Pagani O, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast. 2018;42:41–9. https://doi.org/10.1016/j.breast.2018.08.099.
25. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst. 2018;110(4):426–9. https://doi.org/10.1093/jnci/djx206.
26. Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: are young patients willing to participate in clinical studies? Breast. 2015;24(3):201–7. https://doi.org/10.1016/j.breast.2015.01.005.
27. Anderson C, Engel SM, Mersereau JE, Black KZ, Wood WA, Anders CK, et al. Birth outcomes among adolescent and young adult cancer survivors. JAMA Oncol. 2017;3:1078–84. https://doi.org/10.1001/jamaoncol.2017.0029.
28. Dalberg K, Eriksson J, Holmberg L. Birth outcome in women with previously treated breast cancer-a population-based cohort study from Sweden. PLoS Med. 2006;3:e336. https://doi.org/10.1371/journal.pmed.0030336.
29. Marklund A, Nasiell J, Berger AS, Fagerberg A, Rodriguez-Wallberg KA. Pregnancy achieved using donor eggs in cancer survivors with treatment-induced ovarian failure: obstetric and perinatal outcome. J Women's Health. 2018;27:939–45. https://doi.org/10.1089/jwh.2017.6703.
30. Kranick JA, Schaefer C, Rowell S, Desai M, Petrek JA, Hiatt RA, et al. Is pregnancy after breast cancer safe? Breast J. 2010. https://doi.org/10.1111/j.1524-4741.2010.00939.x.
31. Azim HA, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31:73–9. https://doi.org/10.1200/JCO.2012.44.2285.
32. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2019;37:423–38. https://doi.org/10.1200/JCO.18.01160.