

Impact of ARTs on oncological outcomes in young breast cancer survivors

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STUDY QUESTION: What is the risk of recurrence in young breast cancer survivors who undergo ARTs following completion of anticancer treatment?

SUMMARY ANSWER: ART in breast cancer survivors does not appear to have a negative impact on disease-free survival.

WHAT IS KNOWN ALREADY: In healthy women, fertility treatment does not increase the risk of developing breast cancer. At the time of breast cancer diagnosis and before starting anticancer treatments, several studies have shown the safety of performing ART. However, the safety of ART in breast cancer survivors following completion of anticancer treatment remains under-investigated. In general, breast cancer survivors are counselled to avoid any hormonal treatment but there are limited data available on the effect of short exposure to high oestradiol levels during ART. The largest study in this regard included 25 breast cancer survivors exposed to ART and did not show a detrimental effect of ART on patient survival. Hence, taking into account that pregnancy after breast cancer does not affect cancer prognosis, defining the safety of ART in breast cancer survivors remains a priority.

STUDY DESIGN, SIZE, DURATION: We conducted a retrospective multicentric matched cohort study including a cohort of breast cancer survivors who underwent ART (exposed patients) between January 2006 and December 2016. Exposed patients who were eligible for the study were matched according to known breast cancer prognostic factors. Matched breast cancer survivors did not undergo ART (non-exposed patients) and were disease-free for a minimum time that was not less than the time elapsed between breast cancer diagnosis and first ART for the matched ART-exposed patients.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data were retrieved from all survivors who had been diagnosed with breast cancer in eight participating centres at an age of ≤ 40 years, without metastasis, ongoing pregnancy, pre-existing neoplasia or ovarian failure. ART included ovarian stimulation for IVF/ICSI, clomiphene citrate treatment and hormone replacement therapy for embryo transfer. Data were collected from an oncological database for the selection of breast cancer patients in the non-exposed group. Exposed patients were matched (1:2) for germline BRCA status, tumour stage, anticancer treatment and age, whenever feasible. Matched groups were compared at baseline according to characteristics using conditional logistic regression. Kaplan–Meier curves were constructed to compare time to recurrence between groups, with the time of ART as starting point that has been adjusted in the non-exposed group. The analyses were performed using Stata IC/15.1.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 39 breast cancer patients in the ART group were eligible for the analysis and were matched with 73 controls. There was no statistical difference between the two groups for the presence of *BRCA* mutation, tumour characteristics, use of (neo)adjuvant chemotherapy and of adjuvant endocrine therapy. Exposed patients were younger than non-exposed patients (mean age 31.8 vs 34.3 years, respectively; $P < 0.001$). In the ART group, 89.7% were nulliparous at diagnosis compared to 46.6% of controls ($P < 0.001$). ART was performed at a mean age of 37.1 years old, after a median time of 4.1 years following breast cancer diagnosis (range: 1.5–12.5). Median anti-Müllerian hormone at the time of ART was 0.28 ng/ml (range: 0–4.4) and median serum oestradiol peak level was 696.5 pg/ml (range: 139.7–4130). Median follow-up time from first attempt of ART was 4.6 years (range: 2.4–12.5) in the ART group. Adjusted follow-up time for the non-exposed group was 6.9 years (range: 1.1–16.5 years) ($P = 0.004$). In the ART group, 59% of patients had a pregnancy after breast cancer compared to 26% in the non-exposed patients ($P = 0.001$). Breast cancer relapsed in 7.7% versus 20.5% women in the ART and non-exposed groups, respectively (hazard ratio 0.46, 95% CI 0.13–1.62, $P = 0.23$). Median time to relapse was 1.3 (range: 0.3–2.7) years versus 4.5 (range: 0.4–11.1) years after ART and adjusted time in the ART and non-exposed groups, respectively ($P = 0.14$).

LIMITATIONS, REASONS FOR CAUTION: Although this is the first and largest multicentric study addressing the impact of ART on breast cancer recurrence to provide data on oestrogen exposure, only a small number of patients could be included. This reflects the reluctance of breast cancer survivors and/or oncologists to perform ART, and highlights the need for a prospective data registry to confirm the safety of this approach. This would offer the possibility for these patients, who are at a high risk of infertility, to fully benefit from ART.

WIDER IMPLICATIONS OF THE FINDINGS: Although recent studies have proven that pregnancy after breast cancer has no detrimental impact on prognosis, counselling patients about the safety of ART remains challenging. Our study provides reassuring data on the use of ART in breast cancer survivors with favourable prognostic factors, for when natural conception fails.

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Introduction

Breast cancer is the most commonly diagnosed cancer and the main cause of cancer death in women (Bray et al., 2018). Worldwide, breast cancer accounts for almost one-third of all newly diagnosed cancers in female adolescents and young adults, with 191 055 new diagnoses in 2012 (Fidler et al., 2017). Survival from early breast cancer has improved over the past few years and is now almost 90% at 5 years (Close et al., 2019). This has brought attention to the issue of long-term quality of life, including the possibility of parenthood. Pregnancy has been shown to have no negative impact on prognosis (Hartman and Eslick, 2016; Lambertini et al., 2018a). However, a growing number of young breast cancer survivors are faced with multiple difficulties in achieving pregnancy, which may compromise their quality of life. Chemotherapy-induced ovarian damage and ovarian ageing following protracted hormonal adjuvant therapy dramatically increase the risk of infertility (Howard-Anderson et al., 2012). Due to a general steady trend towards delayed childbearing, the average age at which women give birth now stands at 30 years or above in Organization for Economic Cooperation and Development (OECD) countries (OECD—Social Policy Division—Directorate of Employment, Labour and Social Affairs, 2019). This trend towards

delayed childbearing, combined with the fact that the highest incidence of breast cancer in the young adult population is estimated to occur between 30 and 39 years old (Fidler et al., 2017), has caused a growing number of women to be diagnosed with breast cancer when they have not yet started or completed their families.

Following oncological guidelines, oncofertility specialists should inform women about the gonadotoxicity of (neo)adjuvant treatment and offer fertility preservation strategies (Peccatori et al., 2013; Oktay et al., 2018; Paluch-Shimon et al., 2020). Ovarian stimulation with the use of gonadotropins associated with an aromatase inhibitor was first proposed in 2003 by Oktay et al. (2003) in non-metastatic breast cancer patients to collect and cryopreserve mature oocytes. Despite the off-label use of letrozole in this indication, this approach was largely adopted as a fertility preservation option in breast cancer patients to reduce the serum oestradiol levels associated with ovarian stimulation (Oktay et al., 2005; Ben-Haroush et al., 2011; Meirou et al., 2014; Kim et al., 2016; Moravek et al., 2018; Rodriguez-Wallberg et al., 2018; Letourneau et al., 2020). Although the evidence for the use of this technique was mainly based on small retrospective studies, the protocol appears to be safe when followed by anticancer treatment. As a result, oocyte/embryo cryopreservation is considered to be the standard fertility preservation option in breast cancer patients

(Peccatori *et al.*, 2013; Oktay *et al.*, 2018; Paluch-Shimon *et al.*, 2020). Once in remission, breast cancer survivors who face infertility or premature ovarian insufficiency can resort to ARTs in order to conceive and complete their family plans. However, data on the safety of ART in young breast cancer survivors are scarce, resulting in a reluctance to offer these options.

In the overall population, fertility treatment does not increase the risk of developing breast cancer (Sergentanis *et al.*, 2014; Practice Committee of the American Society for Reproductive Medicine, 2016). However, the use of clomiphene citrate has been associated with an increase in breast cancer risk (Gennari *et al.*, 2015). Moreover, current guidelines contraindicate oestrogen exposure, such as hormonal replacement therapy at menopause in patients with a previous history of breast cancer (Santen *et al.*, 2017). While ovarian stimulation before starting anticancer treatment is considered safe and is recommended by international oncological and fertility guidelines (Peccatori *et al.*, 2013; Martinez, 2017; Oktay *et al.*, 2018; ESHRE Female Fertility Preservation Guideline Development Group, 2020), the safety of ART in breast cancer survivors who are in complete remission remains under investigated. The important question of the safety of ART in breast cancer survivors was first addressed in a multicentric study conducted in 2015 (Goldrat *et al.*, 2015). After screening a large database, the authors reported on the follow-up of a small cohort of 25 breast cancer survivors who underwent ART and subsequently became pregnant (Goldrat *et al.*, 2015). The authors concluded that performing ART in women with a prior history of breast cancer was feasible with no apparent detrimental effect on survival (Goldrat *et al.*, 2015). Recently, in a retrospective, population-based, matched cohort study, 37 breast cancer patients achieved pregnancy and live birth through ART after remission compared to 148 non-exposed patients who gave birth after breast cancer without IVF (Rosenberg *et al.*, 2019). In the ART cohort of that study, eight patients out of 37 (21.6%) were included even though they underwent fertility preservation at the time of diagnosis. Although there were some important limitations, this study did not reveal an increased relapse risk in breast cancer patients who gave birth after ART as no relapses were reported in this group. Nevertheless, concerns remain regarding the safety of performing ovarian stimulation in this setting due to the limited evidence available. Survivors and clinicians are still faced with the clinical dilemma of whether ART may increase the risk of breast cancer recurrence, and fewer than 60% of oncologists are completely reassured regarding the safety of the use of ART in infertile breast cancer survivors (Lambertini *et al.*, 2018b).

The objective of this study was to evaluate disease-free survival in a cohort of breast cancer survivors exposed to ART in comparison to a non-exposed matched population. We aimed to improve our ability to counsel young breast cancer survivors regarding the safety of performing ART after complete remission.

Materials and methods

Study population

Through the Belgian Society of Reproductive Medicine (BSRM) consortium, we invited all fertility centres that have an IVF laboratory to participate in the Art CanCER SurvivorS (ACCESS) study. The

participating centres collected data concerning treated breast cancer patients who underwent ART between January 2006 and December 2016. ART included one or more of the following procedures: ovarian stimulation for IVF/ICSI, clomiphene citrate for uterine insemination or ovulation monitoring, hormone replacement therapy (HRT) for frozen embryo transfer (FET). Inclusion criteria were breast cancer diagnosis between 18 and 40 years of age and in remission at the time of ART. Exclusion criteria included breast cancer diagnosed during pregnancy, metastatic disease, history of any previous neoplasm, history of premature ovarian failure before breast cancer and loss of follow-up within the 2 years following ART. Follow-up data were collected by reviewing all medical records or contacting the oncologists/general practitioners in order to update the follow-up.

Data for non-exposed matched patients were collected in two Belgian oncological centres in Brussels (CUB-Erasme and Institut Jules Bordet), using an existing oncologic database of 781 patients aged <42 years old at diagnosis. Eligible patients were matched (1:2) according to known breast cancer prognostic factors: age range at diagnosis (20–25, 26–30, 31–35, 36–40 years), germline *BRCA* mutation, tumour size (T) and nodal status (N), histological cancer type, hormone receptors, HER2 status, chemotherapy and use and length of adjuvant endocrine treatment. All these criteria were met whenever feasible. If complete matching was not feasible, priority was given to germline *BRCA* mutations, T and N stage and histological characteristics. Breast cancer survivors in the non-exposed group had to be disease-free for a minimum time that was not less than the time elapsing between breast cancer diagnosis and first ART for the matched ART-exposed patients. Matching was performed by a single person (M.C.) and was then reviewed by I.D. The charts from matched non-exposed patients were reviewed in order to check for consistency, verify that they did not attempt to conceive through ART and update the follow-up data.

Statistical analyses

All statistical analyses were performed using Stata IC/15.1. For continuous variables, we present mean and SD for symmetrical distribution, or median and range (minimum–maximum values) for asymmetrical distributions. Matched groups were compared at baseline (breast cancer diagnosis) according to different characteristics using conditional logistic regression. Subgroup analyses were performed with Student's T-test or the Mann–Whitney–Wilcoxon test depending on the distribution. A Kaplan–Meier curve was constructed to compare time to recurrence between groups. In order to compare disease-free survival between the two groups, the starting point was defined as the time of exposure to ART for exposed patients within the matched pair. We adjusted the starting point for non-exposed matched patients according to the time elapsed between breast cancer diagnosis and ART for the exposed patients. Log-rank test was applied. Hazard ratios (HRs) were derived from Cox models.

Ethical approval

This study was approved by the Ethics Committees (EC) of all participating centres. CUB-Erasme acted as the central EC (Approval EC number P2018/377).

Results

Patients included in the study

A total of 17 centres were invited to participate through the BSRM consortium. Four fertility centres did not have any eligible patient or enough data and five centres did not respond. We received anonymized data for 70 patients from eight fertility centres in Belgium. Thirty-nine of them were deemed eligible for the study according to the exclusion and inclusion criteria. Matching 1:2 was feasible for 34 exposed patients. Five patients carrying *BRCA* mutations were matched with only one non-exposed patient, since it was not possible to find more than one patient with similar oncological characteristics, appropriate timing of follow-up and age range in our oncologic centres database. The exclusion criteria and matching process are detailed in Fig. 1.

Patients' oncological characteristics

Exposed patients were 31.8 ± 3.9 years old at diagnosis, while non-exposed patients were 34.3 ± 3.6 years old ($P < 0.001$). No significant difference in age was observed when the population was analysed separately according to the presence of *BRCA* mutations: patients carrying

a *BRCA* germline mutation were aged 30.3 ± 3.2 and 33.5 ± 3.4 years at diagnosis in the exposed and non-exposed groups, respectively ($P = 1$); patients who did not carry *BRCA* mutations were aged 32.1 ± 4.5 and 33.3 ± 3.8 years in the exposed and non-exposed groups, respectively ($P = 0.11$). Patients' matching oncological characteristics and anticancer treatments are summarized in Table I. All patients had ductal invasive breast cancer (100%), with 16/39 (41%) having triple-negative tumours. The median duration of adjuvant endocrine therapy was 5 years (range: 1–10) in the non-exposed patients and 3 years (range: 2–5) in the ART-exposed patients ($P = 0.02$).

A higher proportion of ART-exposed patients had never been pregnant before breast cancer diagnosis compared to the non-exposed group (71.8% vs 41.1%, respectively; $P = 0.004$). Similarly, 89.7% of ART-exposed patients were nulliparous compared to 46.6% of non-exposed patients ($P < 0.001$).

Reproductive outcomes

The characteristics of the ART cohort are reported in Table II. Overall, ART-exposed patients underwent 207 treatment cycles: 107 ovarian stimulation cycles for IVF/ICSI (51.7%), 64 FET using an HRT protocol (30.9%), 18 modified natural cycles (8.7%) and 18

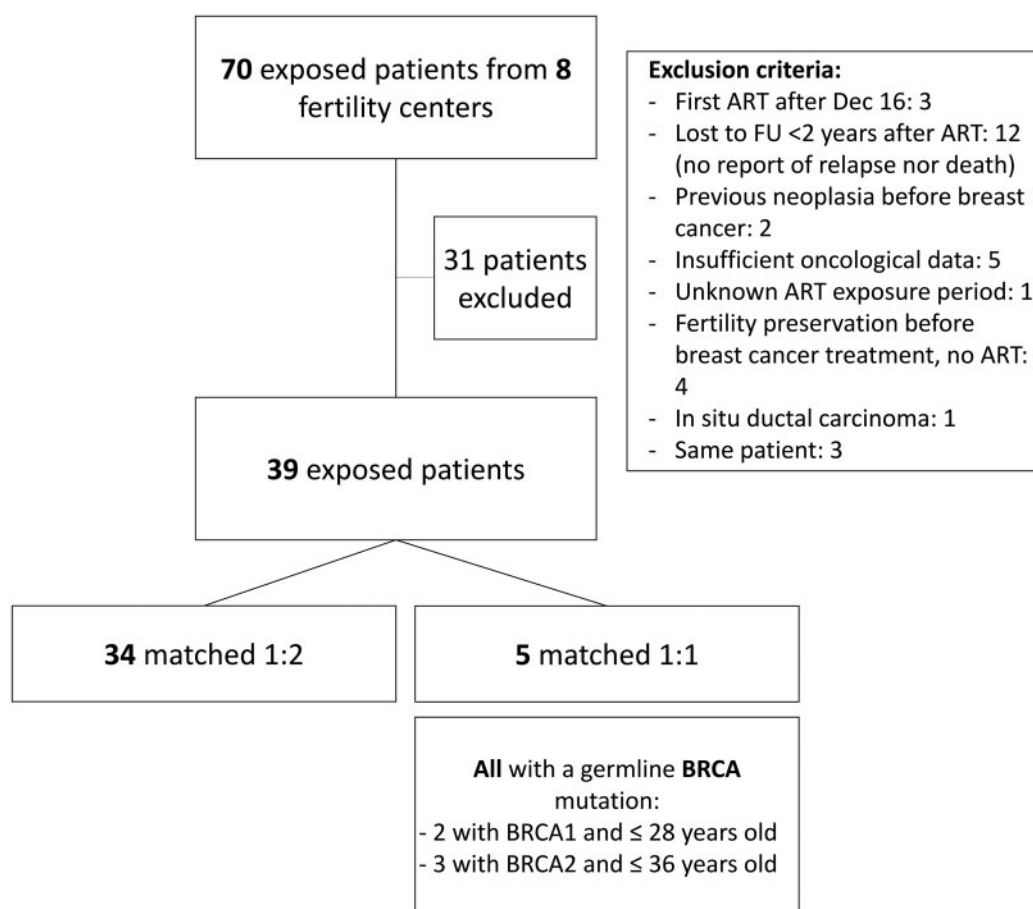


Figure 1. Exposed cohort: exclusion criteria and matching process. FU, follow-up.

Table I Matching oncological characteristics and treatment regimens of exposed and non-exposed patients.

Patients		ART-exposed patients (n = 39) n (%)	Non-exposed patients (n = 73) n (%)	P-value*
Predisposing germline mutation	BRCA negative	18 (46.2)	25 (34.2)	1.00
	BRCA positive	15 (38.5)	25 (34.2)	
	Unknown	6 (15.4)	23 (31.5)	
T stage	Stage 1	26 (66.7)	50 (68.5)	1.00
	Stage 2	8 (20.5)	19 (26.0)	
	Stage 3	1 (2.6)	2 (2.7)	
	Stage 4	1 (2.6)	2 (2.7)	
	Unknown	3 (7.7)	0 (0)	
N stage	0	30 (76.9)	56 (76.7)	1.00
	I	7 (17.9)	17 (23.3)	
	Unknown	2 (5.1)	0 (0)	
Oestrogen receptors	Negative	20 (51.3)	38 (52.1)	0.44
	Positive	17 (43.6)	35 (47.9)	
	Unknown	2 (5.1)	0 (0)	
Progesterone receptors	Negative	19 (48.7)	44 (60.3)	0.34
	Positive	17 (43.6)	29 (39.7)	
	Unknown	3 (7.7)	0 (0)	
HER2	Negative	26 (66.7)	56 (76.7)	0.29
	Positive	10 (25.6)	16 (21.9)	
	Unknown	3 (7.7)	1 (1.4)	
Chemotherapy	Yes	30 (76.9)	66 (90.4)	0.1
	No	7 (17.9)	7 (9.6)	
	Unknown	2 (5.1)	0 (0)	
Hormonal therapy	No	22 (56.4)	40 (54.8)	0.76
	Yes	17 (43.6)	33 (45.2)	

N, node; T, tumour.

*Unknown data were excluded from the analysis.

Table II ART data.

Data at the beginning of the cycles and data for ART	ART-exposed patients (n = 39)	
	n	Data
Median age at ART—years (range)	39	38.3 (27.4–46.7)
Median FSH level—IU/l (range)*	35	10.6 (2.7–200)
Median AMH level—ng/ml (range)*	32	0.28 (0–4.4)
Median serum oestradiol peak during ART—pg/ml (range)**	38	696.5 (139.7–4130)
Type and median number of ART cycle (range)		
IIU or ovulation monitoring with clomiphene citrate	4	4 (1–9)
Natural modified OS cycle	6	1.5 (1–10)
OS for IVF or ICSI	29	3 (1–8)
FET under hormone replacement treatment	21	2 (1–12)

AMH, anti-Müllerian hormone; FET, frozen embryo transfer; IIU, intra-uterine insemination; OS, ovarian stimulation.

*Basal values measured at the beginning of the menstrual cycle.

**Measured at triggering or ovulation.

clomiphene citrate cycles for ovulation induction (8.7%). Eleven patients underwent only ovarian stimulation cycles for IVF/ICSI, with a median number of four cycles per patient (range: 1–7) and a median serum oestradiol at triggering of 1296 pg/ml (range: 151–2601). Eight patients had only FET in HRT cycles, with a median number of two cycles per patient (range: 1–7) and a median serum oestradiol peak of 341 pg/ml (range: 139.7–1347.2). One patient underwent only one clomiphene citrate cycle with a median serum oestradiol peak of 505 pg/ml. Eleven patients underwent both ovarian stimulation cycles for IVF/ICSI and FET in HRT cycles. In these exposed patients, the median serum oestradiol peak was 1046 pg/ml (range: 236–4103).

Conception and livebirth rates after breast cancer were significantly higher in patients who underwent ART (Table III). However, less than 50% of the patients in the ART-exposed group had a livebirth. Out of 73 non-exposed patients, 19 (26.0%) reported spontaneous pregnancies but the total number of patients who attempted pregnancy was not available.

Oncological outcomes

ART-exposed and matched non-exposed patients had a disease-free follow-up of at least as long as the timing between diagnosis and ART. The total follow-up period from diagnosis reached a median of 9.4 (range: 4.5–22.2) and 12.1 (range: 6.8–19.8) years in the ART-exposed and non-exposed groups, respectively. Exposed patients underwent ART in a median time of 4.1 years following breast cancer diagnosis (range: 1.5–12.5). Median time of follow-up from ART was 4.6 years (range: 2.4–12.5) in the exposed patients. Median time of

follow-up from ART adjusted starting point in non-exposed patients was 6.9 years (range: 1.1–16.5) (Table IV). Disease relapse was less frequently observed in ART-exposed patients (3/39) than in non-exposed patients (15/73), but the HR showed no significant difference (HR 0.46, 95% CI 0.13–1.62, $P=0.23$). Among patients who relapsed, median time from ART/ART-adjusted starting time to relapse was 1.3 years (range: 0.3–2.7) in the ART group and 4.5 years (range: 0.4–11.1) in the non-exposed group. Kaplan–Meier curves on time to impending relapse in the ART group and in the non-exposed group did not show any difference in disease-free survival from ART or ART-adjusted starting time ($P=0.22$) (Fig. 2). Five patients from the non-exposed group who became pregnant after breast cancer remission experienced a relapse (5/19). The characteristics of the ART cycles performed in the three patients who relapsed are described in Table V. One of them was a carrier of a *BRCA1* mutation (Patient 3).

Discussion

With more than 8 years of follow-up, this study suggests that the use of ART in breast cancer survivors does not have a detrimental impact on breast cancer recurrence risk. In addition, this study highlights multiple factors complicating the chance to conceive for breast cancer survivors. Baseline fertility characteristics of ART-exposed breast cancer survivors showed they had a low ovarian reserve. This could be the consequence of the gonadotoxic effects of chemotherapy for 76.9% of patients or may be related to the age of these patients when they underwent ART (37.1 years). The most common ART were IVF/ICSI and FET in HRT cycles. As a consequence, the median serum oestradiol peak level during ART was roughly double compared to the peak achieved during a physiological menstrual cycle (Baird and Fraser, 1974).

In a very recent Finnish registry-based study of data from 1993 to 2012, the authors investigated the use of fertility drugs (both for fertility treatment and fertility preservation) in a cohort of 541 female cancer survivors, including 221 breast cancer survivors, as compared to 358 siblings (Melin et al., 2020). They confirmed that fertility drugs were more commonly prescribed in cancer survivors than in siblings (incidence rate ratio 1.43, 95% CI 1.25–1.65), suggesting a higher risk of infertility in this population.

Table III Conception and livebirths following breast cancer treatment.

Patients		ART-exposed patients (n = 39) n (%)	Non-exposed patients (n = 73) n (%)	P-value
Conception	No	16 (41.0)	54 (74.0)	0.001
	Yes	23 (59.0)	19 (26.0)	
Livebirth	No	22 (56.4)	57 (78.1)	0.006
	Yes	17 (43.6)	16 (21.9)	

Table IV Oncological outcomes.

Oncological outcomes		ART exposed patients (n = 39)	Non-exposed patients (n = 73)	P-value
Median follow-up from breast cancer diagnosis—years (range)		9.4 (4.5–22.2)	12.1 (6.8–19.8)	0.004
Median follow-up time from ART/ART-adjusted starting time—years (range)		4.6 (2.4–12.5)	6.9 (1.1–16.5)	0.004
Median time to relapse from ART/ART-adjusted starting time—years (range)		1.3 (0.3–2.7)	4.5 (0.4–11.1)	0.14
Relapse—n (%)	No	36 (92.3)	58 (79.5)	0.10
	Yes	3 (7.7)	15 (20.5)	
Death—n (%)	No	38 (97.4)	73 (100.0)	1.00
	Yes	1 (2.6)	0 (0)	

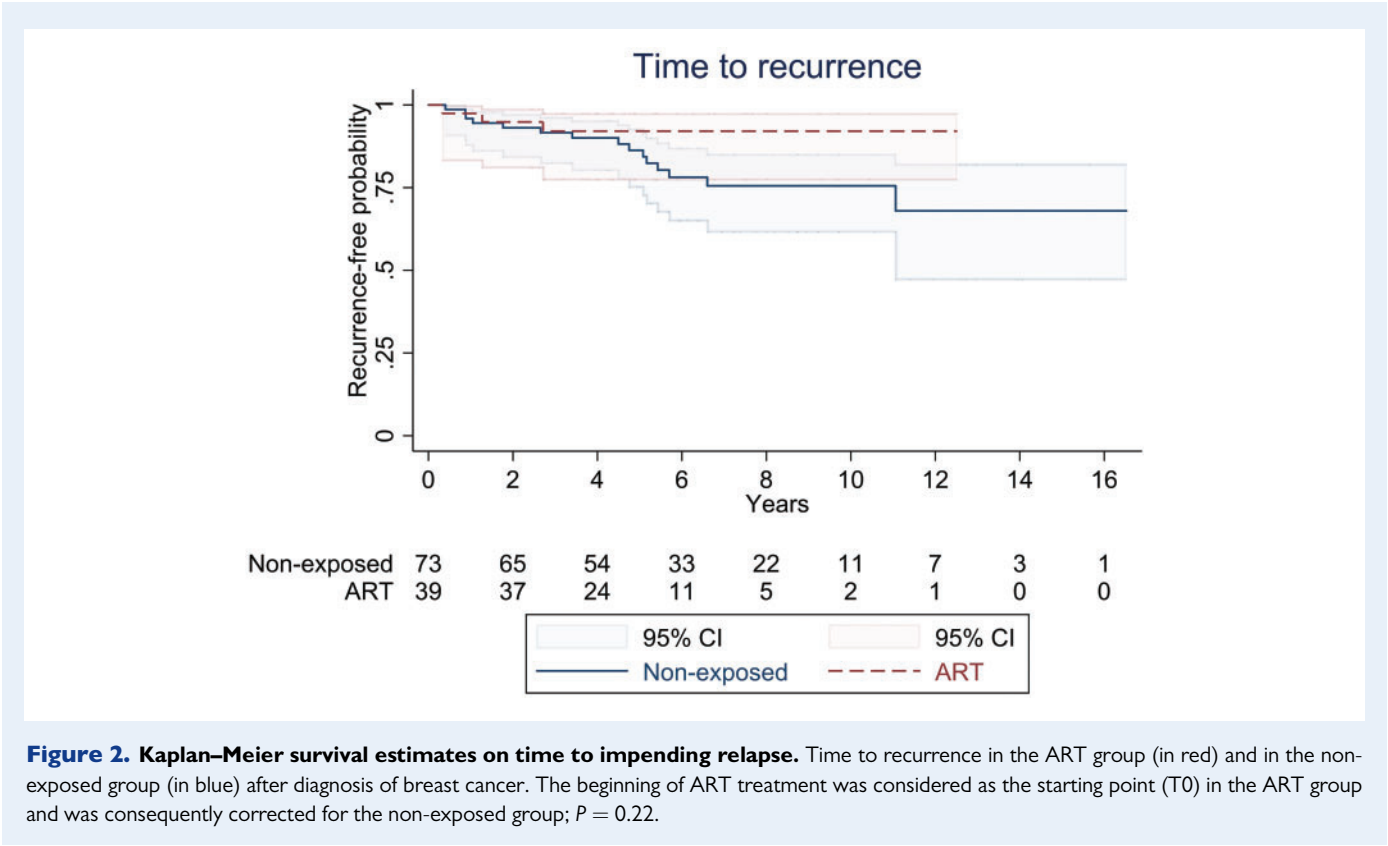


Table V Main oncologic and ART data of exposed patients that experienced a relapse.

Patient	Stage		Hormonal receptors	FSH (IU/l)	AMH (ng/ml)	ART	E2 (pg/ml)	Pregnancy and delivery	Interval between the start of ART and relapse/pregnancy and relapse (years)	Interval between the first breast cancer and the relapse (years)
	T	N								
Patient 1	2	0	Positive	200	<0.1	4 FET in HRT	1347.2	No	1	7
Patient 2	1	0	Positive	66.9	0.1	1 FET in HRT	139.7	One pregnancy and a livebirth	2/2	9
Patient 3	1	0	Positive	17.3	<0.1	2 ovarian stimulations for IVF/ICSI	1700	No	A few months after starting ART	4

AMH, anti-Müllerian hormone; E2, serum oestradiol peak during ART; FET, frozen embryo transfer; HRT, hormone replacement therapy.

A limitation of our study was its retrospective design. Moreover, the study included only a small number of ART-exposed patients. However, exposed and non-exposed patients were matched for most of the oncological prognostic factors and breast cancer characteristics. At diagnosis, non-exposed patients were slightly older compared to the exposed patients (mean age: 34.3 vs 31.8 years old, respectively) but this difference was not significant in comparisons between the *BRCA* carrier and non-carrier populations. Overall, the effect of the difference in age between groups in our population on prognosis is difficult to evaluate but it is possible that age did not influence the disease-free survival of our cohort. Evaluation of large data sets from national cancer registries on the impact of age on prognosis has demonstrated an independent

deleterious effect of age younger than 35 on prognosis (Kroman *et al.*, 2000; Fredholm *et al.*, 2009). However, these studies did not specifically compare the effect of age on prognosis in young adult patients with mean age differences such as those found in our cohort.

Although our cohort was composed of a small number of patients, it is the largest dataset on this topic existing in the literature with the longest follow-up. Moreover, the data were collected from the national consortium of fertility clinics in Belgium that has the second highest number of ART cycles per million inhabitants (De Geyter *et al.*, 2020). Our previous multicentric retrospective study including 198 breast cancer survivors who achieved pregnancies either spontaneously ($n = 173$) or after ART ($n = 25$) did not demonstrate any

difference in relapse rates after an interval between conception and last follow-up of 63 and 50 months, respectively (Goldrat et al., 2015). However, patients who underwent ART had favourable disease characteristics (higher incidence of T stage I–II tumours and node-negative status), as in our present cohort (94.4% stage T I or II, and 81.1% negative nodal status). Less than half of them (43.6%) received adjuvant hormonal therapy. These findings might reflect the caution in advising ART from clinicians (Lambertini et al., 2018b), particularly when more advanced stages of the disease were diagnosed. Importantly, the follow-up was longer and both the ART-exposed and non-exposed groups had similar oncological characteristics in the present study. Moreover, the majority of ART were ovarian stimulation cycles for IVF/ICSI, accounting for 107 cycles out of 207 (51.7%) that exposed the patients to high oestrogen levels (Lambertini et al., 2016). Reassuring data on the safety of IVF in breast cancer survivors were also recently provided from a retrospective registry-based study by Rosenberg et al. (2019). Patients with a diagnosis of breast cancer were cross-matched to those who had delivered following a breast cancer diagnosis and to those who underwent ART. The inclusion period was from 1982 to 2014. As a result, 37 women were exposed to ART drugs: 29 (78%) underwent IVF treatment after cancer treatment while 8 (22%) underwent ART for fertility preservation before anticancer treatment. This mixed cohort was compared to 148 non-exposed patients who delivered but did not receive IVF treatment. Mean follow-up times were around 10 years in both groups. However, there were considerable missing data on cancer characteristics and ART. None of the exposed patients experienced relapse, while 36 (24.4%) relapses were reported among the non-exposed patients ($P = 0.0002$). In our study including 39 breast cancer survivors, ovarian stimulation for IVF was also the most common treatment as 29 patients had at least one cycle (74.4%). In our cohort, even with 43.6% having positive oestrogen receptor tumours, no detrimental impact of ovarian stimulation on disease-free survival was observed. Our data suggest that short exposure to high oestradiol levels during ovarian stimulation (1–2 weeks) has no detrimental effect on oncological outcomes, at least for a median number of ovarian stimulation cycles per patient of 3 (1–8). However, the median ovarian reserve was low in the exposed population, leading to relatively limited exposure to oestradiol during ovarian stimulation. Nevertheless, there was wide variation in the serum oestradiol peak levels. Further studies are required to evaluate the benefits of maintaining low oestradiol levels with aromatase inhibitors in high responder patients during ovarian stimulation.

In conclusion, this study has demonstrated that ART is feasible and does not seem to have a detrimental impact on prognosis in selected breast cancer survivors, even when patients are exposed to supra-physiological oestradiol levels during ovarian stimulation for IVF/ICSI cycles. Based on our data, young breast cancer patients with favourable disease characteristics and prognosis, should not be discouraged from attempting ART in order to become pregnant after the end of anticancer treatment. Nevertheless, large prospective studies are needed to confirm these findings.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

M.C., M.L. and I.D. conceived and designed the work; M.C., M.L., A.D., M.D.V., S.L.F., C.A., A.D., F.V.M., C.W., R.I., E.d.A. and C.C. acquired the data; and J.B. performed the statistical analysis. M.C. and I.D. interpreted the data. M.C. drafted the work and all other authors revised it critically and gave final approval for publication.

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Conflict of interest

M.D.V. is a CooperSurgical scientific advisory board member and receives lecture fees for MSD, Gedeon-Richter and Ferring, outside the submitted work. M.L. has acted as a consultant for Roche and Novartis and has received honoraria from Theramex, Roche, Lilly, Pfizer, Novartis and Takeda, outside the submitted work. I.D. has acted as a consultant for Roche and has received speaker's fees from Novartis, outside the submitted work. E.d.A. has received honoraria and is a Roche/GNE, Novartis, SeaGen and Zodiac scientific advisory board member, has received travel grants from Roche/GNE and GSK/Novartis, and has received research grants from Roche/GNE, Astra-Zeneca, GSK/Novartis and Servier, outside the submitted work. A.D. is a recipient of a research grant from Ferring Pharmaceuticals and receives lecture and/or consultancy fees from Merck, Gedeon-Richter and Ferring Pharmaceuticals, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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