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Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome



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Abstract *Introduction and aims:* We have previously shown that pregnancy is safe following breast cancer, even in endocrine sensitive disease. Yet infertility remains common following systemic treatment. To date, no study has evaluated the safety of assisted reproductive technology (ART) after breast cancer treatment. In this study, we evaluated the impact of ART on pregnancy and long-term outcomes of young breast cancer survivors.

Methods: This is a multi-centre retrospective study in which women who were diagnosed with breast cancer between 2000 and 2009, and had a pregnancy following breast cancer diagnosis were eligible. Patients were divided into two groups according to whether ART following primary systemic therapy was performed to achieve pregnancy. We evaluated the association between ART use and clinic-pathological characteristics, pregnancy outcome and long-term breast cancer outcome.

Results: A total of 198 patients were evaluated; of whom 25 underwent ART. No significant differences in tumour characteristics were observed between both groups, except for histological grade 3 tumours, which were fewer in the ART group (36% versus 59%, $p = 0.033$). Around 90% of patients received primary adjuvant chemotherapy and more than 50% had an endocrine sensitive disease. Patients in the ART group were older at diagnosis (31.4 versus

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33.7 years, $p = 0.009$), at conception (38 versus 35 years, $p < 0.001$), and experienced more miscarriages (23.5 versus 12.6%, $p = 0.082$). Full term pregnancies were achieved in 77% and 76% of the spontaneous and ART groups, respectively. Mean follow-up between conception and last follow-up was 63 and 50 months in the spontaneous and ART groups, respectively with no difference in breast cancer outcome observed between the two groups ($p = 0.54$).

Conclusion: Pregnancy using ART in women with history of breast cancer is feasible and does not seem to be detrimental to cancer outcome. Larger studies are needed to further confirm this observation.

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1. Introduction

Breast cancer is the most frequent malignancy diagnosed in women, occurring in 6–10% of patients during reproductive age [1]. Thanks to advances in adjuvant therapy, recurrence and survival rates have greatly improved over the last decades [2]. Currently around 65–70% of young breast cancer patients are alive and free of distant relapse at 10-years following diagnosis [3]. Hence, we are currently more faced with the need to address quality of life issues of young breast cancer survivors, including the wish to start or complete their family [4].

Several studies and meta-analyses have addressed the safety of pregnancy following breast cancer [5–7]. More recently, a large study by our group has demonstrated for the first time the safety of this approach in women with endocrine-sensitive disease [8]. Moreover, early termination of pregnancy does not appear to reduce the risk of relapse [5,8]. However, current systemic therapies frequently impair patients' fertility albeit a large fraction of them recover their menstrual cycles after completing primary systemic therapy [9]. This results in physicians and patients enquiring into the feasibility and safety of using assisted reproductive technology (ART) in women with history of breast cancer, in order to conceive. To date, no single study has evaluated the impact of ART to achieve pregnancy on cancer outcome.

In this study, we evaluate for the first time the effect of using ART on recurrence and death rates in patients who were previously treated for breast cancer and became subsequently pregnant.

2. Patients and methods

Five European Oncological and Fertility Centers participated in this retrospective study: Institut Jules Bordet (Brussels), Erasme Hospital (Brussels), European Institute of Oncology (Milan), Macerata Hospital (Macerata) and Hospital Val d'Hebron (Barcelona) in addition to the Danish Breast Cancer Cooperative Group (DBCCG). Some of these patients were included in a previous study in which we evaluated the safety of pregnancy following endocrine receptor positive breast

cancer. Yet data on ART were not available at the time [8]. This study was approved by the Ethics committees of all participating centres including Erasme Hospital, which acted as the central ethics committee (Approval number P2013/265).

2.1. Patient population

Eligible patients were women aged 18–45 years, who were diagnosed with primary non-metastatic breast cancer between 2000 and 2009 and subsequently became pregnant (Fig. 1). The cohort was divided into two groups according to whether pregnancies occurred spontaneously (Spontaneous Group) or after ART (ART Group). ART procedures included ovulation induction (clomiphene citrate, gonadotropins) associated with intercourse or intra-uterine insemination (IUI), controlled ovarian stimulation (COS) with gonadotropins for *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI), and egg donation. All ART procedures were performed after completion of standard adjuvant therapy. During the study period, none of the participating centres routinely offered oocyte or embryo cryopreservation before initiating primary systemic therapy for fertility preservation of young breast cancer patients.

2.2. Data collection

The databases of all participating centres and the DBCCG were screened. The patient's oncologist, gynaecologist or family doctors were contacted in order to complete the information on the oncological and pregnancy outcomes, if needed. Data were collected on clinico-pathological characteristics, breast cancer treatment (date of diagnosis, histological type, histological grade, tumour size, nodal status, endocrine receptor status, human epidermal growth factor receptor 2 (HER2) status, type of breast surgery, chemo- and endocrine therapies), fertility treatments (ovulation induction, ovarian stimulation for IVF and oocyte donation) and pregnancy-related information (age at conception, number of pregnancies, and pregnancy outcome). Patients with less than 12 months of follow-up after pregnancy were excluded.

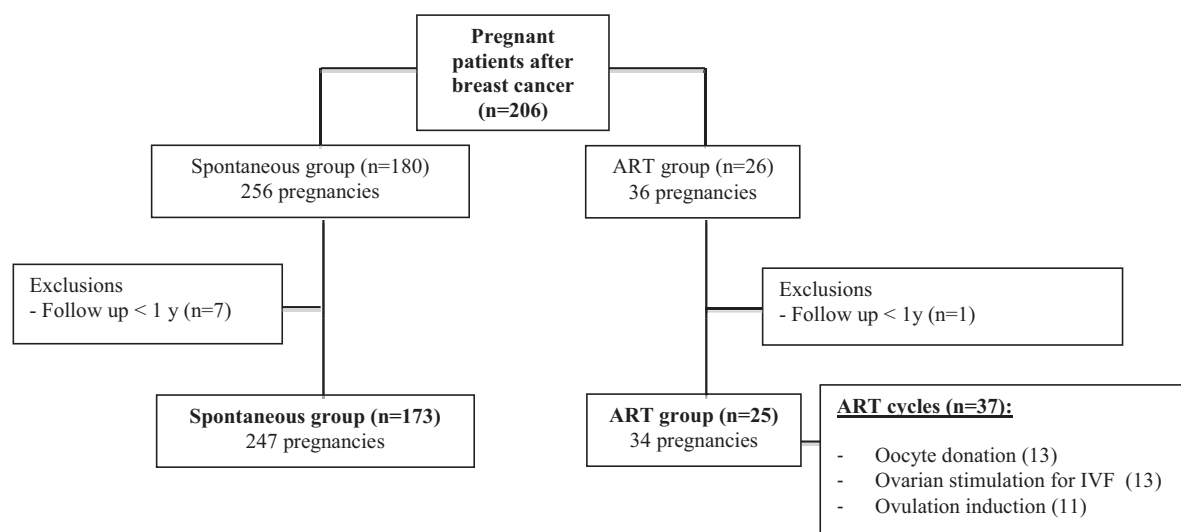


Fig. 1. Study flow chart.

2.3. Statistical analysis

Means were compared using the Student *t*-test. We used an exact Chi-2 test for frequency comparisons. Descriptive statistics was used to examine differences in cancer-related events between the ART and spontaneous pregnancy groups. Cancer related events were defined as breast cancer recurrence (local, or distant) or secondary primary cancers. We also evaluated the difference in death rates between both groups. Statistical analysis was performed using SPSS 22 on Mac OS X. A *p*-value <0.05 was considered significant.

3. Results

A total of 206 women who became pregnant after breast cancer diagnosis were included in this study (Fig. 1). Among those, 180 conceived spontaneously, resulting in 256 pregnancies, whereas 26 patients conceived after ART, resulting in 36 pregnancies. Oocyte donation was the most common procedure, followed by ovarian stimulation for IVF and ovulation induction. We excluded seven and one patients in the spontaneous and ART groups, respectively, due to follow-up of less than 12 months resulting in 247 spontaneous and 34 ART pregnancies, which were evaluable in this study.

Patients' characteristics are summarised in Table 1. Patients in the spontaneous pregnancy group were younger (mean age: 31.2 versus 33.7, *p* = 0.009) and had a higher frequency of histological grade 3 tumours (59.6% versus 36%, *p* = 0.033). On the other hand, patients in the ART group had more node-negative, oestrogen receptor (ER)-positive tumours and shorter duration of endocrine therapy; however, these differences did not reach statistical significance.

3.1. Pregnancy outcomes

Table 2 summarises pregnancy-related information in both groups. Age at conception was significantly higher in the ART than in the spontaneous group (38.5 versus 35.3 years, *p* < 0.001). The majority of pregnancies ended at term in both groups. As expected, no induced abortion was reported in the ART group while 9.7% of patients who had a spontaneous pregnancy underwent induced abortion. We observed tendency of higher miscarriage rate and twin pregnancy in the ART than in the spontaneous group; 23.5% versus 12.6%, *p* = 0.08 and 7.7% versus 3.2%, *p* = 0.24, respectively.

3.2. Impact of ART on breast cancer outcome

Patients had a long-term follow-up in the range of 9 and 8.5 years from breast cancer diagnosis and 5 and 4 years from conception, in the spontaneous and ART groups, respectively. No significant differences in breast cancer outcome were observed between both groups (*p* = 0.54, Table 3). Ten (5.7%) and two (8%) patients developed distant recurrences in the spontaneous and ART groups respectively. Contralateral breast cancer was reported in seven patients; all in the spontaneous pregnancy group.

Eleven patients died in the spontaneous group (6.4%). Only one patient died in the ART group secondary to distant recurrence, which occurred 14 months after conception.

4. Discussion

Over the last two decades, there has been much debate over cancer risk induced by infertility drugs. In 2010, a meta-analysis including 15 cohort- and eight

Table 1
Patients' characteristics.

	Spontaneous pregnancy Group, <i>N</i> = 173 (%)	ART pregnancy group, <i>N</i> = 25 (%)	<i>P</i> value
Age at diagnosis (years)			0.009
Mean	31.4	33.7	
Interquartile range	29–34	31–37	
Histological type			0.34
Invasive ductal carcinoma	158 (91.3)	21 (84)	
Other histologies*	14 (8.1)	4 (16)	
Unknown	1 (0.6)	0	
Histological grade			0.03
1	16 (9.2)	5 (20)	
2	43 (24.8)	10 (40)	
3	103 (59.6)	9 (36)	
Unknown	11 (6.4)	1 (4)	
Tumour size			0.36
T ₁ –T ₂	158 (91.3)	25 (100)	
T ₃ –T ₄	10 (5.8)	0	
Unknown	5 (2.5)	0	
Node status			0.12
Positive	73 (42)	6 (24)	
Negative	100 (58)	19 (76)	
Oestrogen receptor status			0.19
Positive	91 (52.6)	17 (68)	
Negative	82 (47.4)	8 (32)	
HER2 status			0.48
Positive	48 (27.7)	6 (24)	
Negative	89 (51.4)	18 (72)	
Unknown	36 (20.8)	1 (4)	
Surgery type			0.50
Radical mastectomy	62 (35.8)	7 (28)	
Conserving surgery	111 (64.2)	18 (72)	
Endocrine therapy			0.09
Yes	76 (43.9)	16 (64)	
No	91 (52.6)	9 (36)	
Unknown	6 (3.5)		
Median endocrine therapy duration (mo)	48	33	0.06
Interquartile range	30–60	24–44	
Chemotherapy			0.40
Adjuvant	118 (68.2)	15 (60)	
Neo-adjuvant	41 (23.7)	7 (28)	
No chemotherapy	3 (1.7)	1 (4)	
Unknown	11 (6.4)	2 (8)	

* Other histologies include invasive lobular carcinoma, medullary carcinoma, mucinous carcinoma; ART, assisted reproductive therapy; HER2, human epidermal growth factor receptor 2; mo, months.

case-control studies somehow settled the argument by showing no significant association between different ART therapies (clomiphene, gonadotropins, gonadotropins releasing hormones and unspecified agents) and the risk of developing breast cancer [10].

On the other hand, only scarce data are available on infertility management in previously treated breast cancer survivors. A few published case-reports have described ovarian stimulation for IVF in a total of five breast cancer patients after completion of their treatment (Table 4). Two patients underwent three ovarian stimulations for IVF, resulting in two term pregnancies

[11,12]. Three other patients underwent eight IVF treatments after grafted cryopreserved ovarian tissue for fertility restoration [13–15]. Only one of these patients became pregnant with twins. One successful case of oocyte donation after breast cancer treatment was also reported [16]. Short-term follow-up after pregnancy was available for only one patient, with no evidence of relapse [12].

The current study is the first attempt to evaluate the feasibility and safety of pregnancy using ART in previously treated breast cancer patients, with long-term follow-up. A total of 198 women were included over a

Table 2
Pregnancy outcomes.

	Spontaneous pregnancy group, <i>N</i> = 247 (%)	ART pregnancy group, <i>N</i> = 34 (%)	<i>P</i> value
Mean age at conception (years)	35.3	38.5	<0.001
Interquartile range	33–38	34–43	
Median time from diagnosis to conception (mo)	42	48	0.01
Interquartile range	24–63	36–84	
Outcomes			0.08
Miscarriage	31 (12.6)	8 (23.5)	
Induced abortion	24 (9.7)	0	
Term pregnancy	190 (76.9)	26 (76.5)	
Other*	2 (0.8)	0	
Live birth	<i>N</i> = 190	<i>N</i> = 26	0.24
Single	184 (99.8)	24 (92.3)	
Twins	6 (3.2)	2 (7.7)	

ART, assisted reproductive technology; mo, months.

* Other: 1 extra-uterine pregnancy; 1 molar pregnancy.

Table 3
Long-term survival outcome.

	Spontaneous pregnancy group, <i>N</i> = 173 (%)	ART pregnancy group, <i>N</i> = 25 (%)	<i>P</i> value
Interval diagnosis-last clinical FU (mo)	107	102	0.50
Interquartile range	81–131	85–123	
Interval conception-last clinical FU (mo)	63	50	0.06
Interquartile range	37–89	27–72	
Cancer related events (%)	28 (16)	2 (8)	0.54
Local recurrence	8 (4.6)	0	
Distant recurrence	10 (5.7)	2 (8)	
Contralateral breast cancer	7 (4)	0	
2nd primary cancer (non-breast)	3 (1.7)	0	
Death (<i>n</i>)	11 (6.3)	1 (4)	

ART, assisted reproductive technology; FU, follow-up; mo, months.

Table 4
Previously published case-reports on assisted reproductive technology after breast cancer treatment.

References	<i>N</i>	ER status	IVF cycles (<i>n</i>)	Pregnancy	Follow-up
Das et al. [11]	1	Negative	1	Yes	No
El Hussein et al. [12]	1	Unknown	2	Yes	Yes
Kim et al. [13]	1	Positive	2	No	Unknown
Sanchez-Serrano et al. [14]	1	Negative	4	Yes	No
Schmidt et al. [15]	1	Unknown	2	No	No

ER, oestrogen receptor; IVF, *in vitro* fertilisation.

period of nearly 10 years. Among those pregnant women, only 25 (12.6%) reported pregnancies following ART. The small fraction of the ART group may suggest that ART procedures were not encouraged or routinely accessible to breast cancer patients in the early 2000s. Yet it should be noted that this figure may be underestimated as we only included patients who became pregnant and not those who had ART but did not achieve pregnancy. Interestingly, we observed that women who underwent ART had somehow more favourable

prognostic parameters, suggesting that physicians were probably more selective in offering ART to patients with relatively good prognosis. This underscores the uncertainty and fear of the safety of ART in women with history of breast cancer.

Currently young breast cancer patients are advised to preserve their fertility before initiating primary systemic therapy [17,18]. Oocyte or embryo vitrification is considered the procedure of choice, yet it requires controlled ovarian stimulation, which results in increased estradiol

levels. Oktay and co-workers have published a series of studies showing that the use of letrozole along with gonadotropins is associated with relatively low estradiol peaks, sufficient oocyte yield and does not result in increase in breast cancer recurrence, when tested in a prospective trial [19,20]. Meirow and co-workers have recently published similar results with the concomitant use of tamoxifen and gonadotropins [21]. Nonetheless, some young patients do not undergo fertility preservation procedures before initiation of systemic therapy for several reasons including lack of time for ovarian stimulation, ambivalent feelings about future pregnancy while facing a life threatening disease, and in some cases for insurance and/or economical limitations. Even if the majority of patients recover menstrual function after completion of chemo- and endocrine therapy, they may be potentially infertile or with compromised ovarian reserve [9], thus making spontaneous conception not feasible. The current study represents the only evidence to date to describe the feasibility and potential safety of ART in patients who have been previously treated with systemic therapy and wish a subsequent pregnancy.

We found a trend of earlier discontinuation of endocrine therapy and a higher rate of early pregnancy losses in the ART group. We believe that this could be due to higher age at diagnosis and conception in the ART compared to the spontaneous group [22,23]. Old age is associated with higher infertility risk, leaving women no choice but to early-discontinue endocrine therapy and turn to fertility clinics for assisted reproduction [24]. This is becoming more challenging in clinical practice given the recent data suggesting that extended endocrine therapy is offering superior benefits in terms of disease-free and overall survival [25,26]. However, compliance to endocrine therapy in younger women has been shown to be low, largely secondary to quality of life issues, including fertility concerns [27,28]. Hence, there is a need to adopt tailored strategies to address such concerns without compromising the outcome of these patients by offering a suboptimal therapy [29]. In this regard, a large multi-centre international study has just been launched investigating the safety of temporary interruption of endocrine therapy to allow pregnancy in young ER-positive breast cancer patients (POSITIVE, clinicaltrials.gov: NCT02308085).

Our study has some limitations that should be taken into account when interpreting its results. Information was lacking on fertility drugs used and protocols for IVF or oocyte donation, as well as hormonal levels achieved. Patient's parity and fertility history was not assessed, which could have influenced decisions for subsequent pregnancy and the way to attain it. Finally, the study had limited statistical power to reliably estimate the impact of ART on the risk of recurrence. However it is important to acknowledge that it is very challenging

and sometimes not feasible to conduct prospectively powered studies to address such questions and hence we believe that this study is an important attempt to understand the potential safety of ART in previously treated young breast cancer patients.

In conclusion, this is the first study to address the safety and outcome of pregnancy using ART after primary systemic treatment for young breast cancer patients. Our results indicate lack of a detrimental effect of attaining pregnancy via ART on the risk of recurrence in women with history of breast cancer. While the number of patients included in the study is relatively small, warranting further confirmation, we believe this study would provide physicians with important guidance when counselling their patients in the daily practice.

Conflict of interest statement

None declared.

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