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Original research

Assisted reproductive technology in young *BRCA* carriers with a pregnancy after breast cancer: An international cohort study

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ABSTRACT

Introduction: Very limited data exist on assisted reproductive technology (ART) use in *BRCA1/2* carriers conceiving after breast cancer. This study aimed to investigate the safety of ART to achieve a pregnancy after breast cancer in *BRCA1/2* carriers.
Methods: This is an international, hospital-based, retrospective cohort study including *BRCA*1/2 carriers with a pregnancy after prior breast cancer diagnosis at ≤ 40 years of age between 2000 and 2020. Outcomes were compared between young *BRCA1/2* carriers who conceived using ART and those who conceived spontaneously.
Results: Among 543 *BRCA*1/2 carriers with a pregnancy after breast cancer, 436 conceived spontaneously and 107 using ART. Of 107 pregnancies achieved with ART, 45 (42.1 %) were obtained using oocytes/embryo cryopreserved at diagnosis, 33 (30.8 %) after controlled ovarian stimulation for in-vitro-fertilization/intracytoplasmic sperm injection or ovulation induction for intrauterine insemination or planned intercourse after anticancer treatments, 21 (19.6 %) after oocyte donation, while for 8 (7.5 %) patients type of ART was missing. Compared to patients in the no-ART group, those in the ART group were older at the time of conception, had more frequently hormone receptor-positive breast cancer and a longer median time from cancer diagnosis to conception. At a median follow-up of 5.2 years after conception, no apparent detrimental effect of ART on disease-free survival was observed (adjusted HR=0.72, 95 % CI 0.39–1.34).
Conclusion: In young *BRCA1/2* carriers with a pregnancy after breast cancer, ART use did not appear to be associated with increased risk of DFS events.

1. Introduction

Fertility preservation, especially controlled ovarian stimulation (COS) for oocyte/embryo cryopreservation prior to chemotherapy, is standard of care for young women affected by breast cancer [1–3]. Pregnancy after appropriate treatment and follow-up of breast cancer does not appear to affect prognosis [4], including in women with hormone receptor-positive disease [5] and in those harbouring germline *BRCA1/2* pathogenic or likely pathogenic variants (PVs) [6–8].

Over the past years, increasing evidence has shown the safety of assisted reproductive technology (ART) performed before or after anticancer treatments in patients with a history of breast cancer [9–13]. The results of a meta-analysis including 15 studies, of which four looked at safety of ART after anticancer treatments, were reassuring [12]. However, the evidence on the use and safety of ART in patients with breast cancer harbouring germline *BRCA1/2* PVs is very limited [11,14,15]. Addressing the safety of ART is critical for all young patients who are unable to conceive spontaneously after treatment for breast cancer and that may need to rely on ART to achieve a pregnancy [4,11,16–18].

Preclinical data suggest that the presence of *BRCA1/2* PVs may adversely affect fertility through the accumulation of deoxyribonucleic acid (DNA) damage secondary to inadequate DNA repair, resulting in cell apoptosis and accelerated ovarian aging [19–21]. Furthermore, due to the primary function of *BRCA* tumour suppressor genes, it has been hypothesized that the negative impact of gonadotoxic therapies on the ovarian reserve of *BRCA1/2* carriers could be more severe, thus resulting in an increased risk of gonadotoxicity and subsequent infertility [21,22]. However, results of clinical studies on the potential risk of reduced ovarian reserve at diagnosis or after treatment and/or ovarian response to COS in *BRCA1/2* carriers are controversial and no definitive conclusions can be currently made [23].

For these reasons, and taking into account that many concerns remain among physicians in this regard [24], it is of paramount importance to investigate if the need for ART use in *BRCA1/2* carriers may negatively impact on their cancer prognosis. In our previous work including 1252 *BRCA1/2* carriers, out of 168 women with a pregnancy after breast cancer, 22 were achieved through ART [14]. The number of included patients in the ART group was too small to allow any statistical comparison with the no-ART group. Here, we present an update of the previous study with a larger cohort of young *BRCA1/2* carriers with breast cancer. The aim of this analysis was to investigate the safety of ART use in young *BRCA1/2* carriers who had a pregnancy after breast cancer.

2. Materials and methods

This was a retrospective, international, multicentre cohort study including women diagnosed at age ≤ 40 years with invasive breast cancer between January 2000 and December 2020 carrying known germline PVs in *BRCA1* and/or *BRCA2* genes (ClinicalTrials.gov ID NCT03673306) [8]. For the present analysis, only patients who became pregnant after breast cancer were included. Patients who experienced a disease-free survival (DFS) event before becoming pregnant as well as those without data on method of conception (spontaneous or using ART) were excluded.

Young *BRCA1/2* carriers with a pregnancy were stratified into two groups: women who conceived using ART (ART group) and those who conceived spontaneously (no-ART group). ART treatments included COS to cryopreserve oocytes/embryos at breast cancer diagnosis (fertility preservation strategy), COS for *in-vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) or ovulation induction for intrauterine insemination or planned intercourse after anticancer treatments, and oocyte donation.

The analysis aimed to evaluate the safety of ART in young *BRCA1/2* carriers with a pregnancy after breast cancer. The following survival endpoints were considered: DFS, breast cancer specific survival (BCSS)

and overall survival (OS). We also assessed the obstetric and fetal outcomes of the pregnancies. Survival endpoints were defined as previously reported [8].

The coordinator and sponsor of the study was the Institut Jules Bordet (Brussels, Belgium) which also acted as the central ethics committee. Where required, the study also received ethical approval from the local, regional, or national ethics committee of the participating centres.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed to report this work [25].

2.1. Statistical analyses

Numbers and percentages were used for categorical variables, while median and interquartile range were used for continuous variables. The baseline patient and oncological characteristics between the ART and no-ART groups were compared using Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables.

All survival endpoints were calculated from the time of conception. Event rates for DFS, BCSS and OS were calculated as the ratio of the total number of events to the total of the observation times. Kaplan-Meier curves were used to present results for the ART and no-ART groups. Cox proportional hazard models were applied to calculate unadjusted and adjusted hazard ratios (HRs) with 95 % confidence intervals (CIs). Adjustments in survival models were performed for risk-reducing mastectomy and risk-reducing salpingo-oophorectomy (as time-dependent covariate) and for propensity score. The propensity score was calculated using logistic regression to estimate the propensity to use ART, taking into account the variables differently distributed in the two groups (ie age and parity at diagnosis, year of diagnosis, region, specific *BRCA* gene, tumor grade and hormone receptor status).

In a secondary analysis, the ART group was divided into three groups according to the type of ART procedure that was performed: 1) COS at diagnosis (ART at diagnosis); 2) COS or ovulation induction after anticancer treatments (ART after anticancer treatments); 3) oocyte donation. DFS, BCSS and OS events of each ART groups were separately assessed and compared with those of patients who had a spontaneous conception.

A 2-sided p value < 0.05 was defined as statistically significant. Analyses were performed using Stata, software version 16.1 (StataCorp LLC, College Station, TX, USA).

3. Results

Of the 4732 young *BRCA1/2* carriers included from 78 centres worldwide, 659 women had a pregnancy after breast cancer (Figure 1). Among them, 543 were eligible for this specific analysis of whom 107 underwent ART treatments to achieve a pregnancy (ART group) and 436 became pregnant spontaneously (no-ART group). The most commonly used ART technique to achieve a pregnancy was COS for oocyte/embryo cryopreservation at diagnosis (45, 45.5 %), followed by COS or ovulation induction after anticancer treatments (33, 33.3 %), and oocyte donation (21, 21.2 %). For eight pregnancies, the type of ART was missing.

As reported in Table 1, compared to *BRCA1/2* carriers in the no-ART group, those in the ART group were older (median age: 32 vs. 30 years, $p < 0.001$) and more likely to be childless (71.8 % vs. 51.5 %, $p < 0.001$) at cancer diagnosis. The majority of patients in both groups had node negative disease (61.6 % and 66.3 %). Patients in the ART group were more likely to have hormone receptor-positive (43.4 % vs. 30.8 %, $p = 0.016$) or HER2-positive (9.5 % vs. 4.1 %, respectively, $p = 0.044$) disease than those in the no-ART group. Most of the patients in both ART and no-ART groups received chemotherapy (93.5 % and 92.9 %, respectively, $p = 1.0$). During follow-up and after pregnancy,

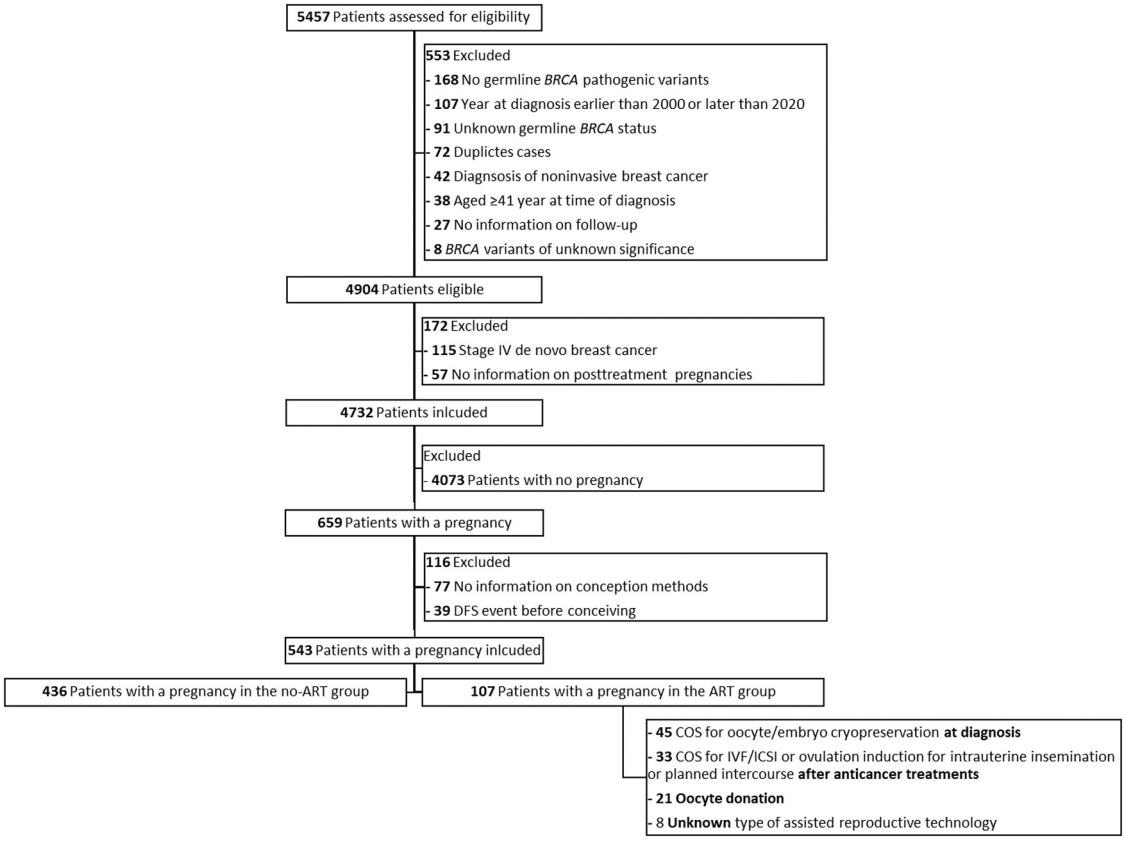

Fig. 1. Participants flow. Legend abbreviations: ART, assisted reproductive technology; COS, controlled ovarian stimulation; DFS, disease-free survival; ICSI, intracytoplasmic sperm injection; IVF, *in-vitro-fertilization*.

Table 1
Baseline patient, tumor and treatment characteristics.

	ART group n = 107	No-ART group n = 436	P-value
Median age at diagnosis, y (IQR)	32 (29–35)	30 (28–33)	<0.001
Parity at diagnosis, n (%)	n = 103	n = 408	<0.001
-0	74 (71.8)	210 (51.5)	
-≥ 1	29 (28.2)	198 (48.5)	
-Missing, n	4	28	
Region of diagnosis, n (%)	n = 107	n = 436	0.494
-North America	11 (10.3)	34 (7.8)	
-South-Central America	2 (1.9)	7 (1.6)	
-Asia	24 (22.4)	71 (16.3)	
-Oceania	2 (1.9)	18 (4.1)	
-Northern Europe	20 (18.7)	73 (16.7)	
-Southern Europe	44 (41.1)	216 (49.5)	
-Eastern Europe	4 (3.7)	17 (3.9)	
Year at diagnosis, n (%)	n = 107	n = 436	0.006
-2000–2005	10 (9.3)	83 (19.0)	
-2006–2010	24 (22.4)	135 (31.0)	
-2011–2015	47 (43.9)	136 (31.2)	
-2016–2020	26 (24.3)	82 (18.8)	
Type of *BRCA* gene, n (%)	n = 107	n = 434	0.413
-*BRCA1*	76 (71.0)	325 (74.9)	
-*BRCA2*	30 (28.0)	107 (24.6)	
-*BRCA1/2*	1 (0.9)	2 (0.5)	
-Unknown if *BRCA1* or *BRCA2*, n	0	2	
Tumor histology, n (%)	n = 106	n = 419	0.429
-Ductal carcinoma	94 (88.7)	375 (89.5)	
-Lobular carcinoma	3 (2.8)	3 (0.7)	
-Mixed ductal/lobular	1 (0.9)	4 (0.9)	
-Invasive, not specified	3 (2.8)	17 (4.1)	
-Other	5 (4.7)	20 (4.8)	
-Missing, n	1	17	
Tumor grade (G),[a] n (%)	n = 99	n = 402	0.213
-G1	1 (1.0)	7 (1.7)	
-G2	26 (26.3)	75 (18.7)	
-G3	72 (72.7)	320 (79.6)	
-Missing, n	8	34	
Tumor size (T),[b] n (%)	n = 104	n = 419	0.104
-T1 (≤2 cm)	55 (52.9)	177 (42.2)	
-T2 (>2 to ≤5 cm)	36 (34.6)	191 (45.6)	
-T3 (>5 cm) to T4	13 (12.5)	51 (12.2)	
-Missing, n	3	17	
Tumor nodal status (N),[b] n (%)	n = 104	n = 424	0.635
-N0	69 (66.3)	261 (61.6)	
-N1	26 (25.0)	126 (29.7)	
-N2 to N3	9 (8.6)	37 (8.7)	
-Missing, n	3	12	
Hormone receptor status, n (%)	n = 106	n = 428	0.016
-ER and PR negative	60 (56.6)	296 (69.2)	
-ER and/or PR positive	46 (43.4)	132 (30.8)	
-Missing, n	1	8	
Tumor HER2 status, n (%)	n = 105	n = 416	0.044
-HER2 negative	95 (90.5)	399 (95.9)	
-HER2 positive	10 (9.5)	17 (4.1)	
-Missing, n	2	20	
Therapy, surgery, n (%)	n = 104	n = 430	0.259
-BCS	50 (48.1)	206 (47.9)	
-Mastectomy	53 (51.0)	224 (52.1)	
-None	1 (1.0)	0 (0.0)	
-Missing, n	3	6	
Therapy, chemotherapy, n (%)	n = 107	n = 436	1.000
-Yes	100 (93.5)	405 (92.9)	
-No	7 (6.5)	31 (7.1)	
Chemotherapy, type, n (%)	n = 99	n = 395	0.118
-Anthracycline- + taxane-based	79 (79.8)	271 (68.6)	
-Anthracycline-based	14 (14.1)	98 (24.8)	
-Taxane-based	3 (3.0)	11 (2.8)	
-Other	3 (3.0)	15 (3.8)	
-Missing, n	1	10	
Therapy, endocrine therapy,[c] n (%)	n = 45	n = 132	0.755
-Yes	41 (91.1)	122 (92.4)	
-No	4 (8.9)	10 (7.6)	
-Missing, n	1	0	
Type of endocrine therapy,[d] n (%)	n = 40	n = 122	0.713
-Tamoxifen + GnRHa	16 (40.0)	53 (43.4)	
-Tamoxifen	11 (27.5)	38 (31.1)	
-Tamoxifen and AI ± GnRHa	6 (15.0)	9 (7.4)	
-AI ± GnRHa	5 (12.5)	16 (13.1)	
-GnRHa	2 (5.0)	4 (3.3)	
-Other	0 (0.0)	2 (1.6)	
-Missing, n	1	0	
Median duration of endocrine therapy, months (IQR)	48 (24–60)	49 (24–60)	0.434
-Missing	5	29	

Abbreviation: AI, aromatase inhibitor; ART, assisted reproductive technology; BCS, breast conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; GnRHa, gonadotropin-releasing hormone agonist; PR, progesteron receptor; y, years.

[a] Histologic grade was based on the degree of tumor histologic differentiation.

[b] Tumor size and nodal status were assessed clinically for patients who received neoadjuvant systemic therapy and pathologically for those who received breast surgery as first treatment.

[c] Percentages were calculated including only patients with hormone receptor-positive breast cancer.

[d] Percentages were calculated including only patients with hormone receptor-positive breast cancer who received adjuvant endocrine therapy.

226 (41.6 %) patients underwent risk-reducing salpingo-oophorectomy, 56 (52.3 %) in the ART group and 170 (39.1 %) in the no-ART group. Risk reducing mastectomy was performed in 78 (72.9 %) and 268 (61.5 %) patients in the ART and no-ART groups, respectively.

3.1. Reproductive outcomes

Reproductive outcomes in the ART group and no-ART groups are reported in Table 2. As compared to patients in the no-ART group, those in the ART group were older at the time of conception (median age: 37.1 vs. 34.3 years, $p < 0.001$) and had a longer median time between cancer diagnosis and conception (4.2 vs. 3.3 years, $p = 0.004$). No statistically significant differences in pregnancy complications were observed between the ART and no-ART groups ($p = 0.220$). Overall, 81.6 % of patients in the ART group and 87.0 % of those in the no-ART group did not report complications. Patients in the ART group had numerically more miscarriages (11.3 % vs. 8.8 %) and fewer induced abortions (0.9 % vs. 8.3 %) than those in the no-ART group.

3.2. Oncological outcomes

As the type of ART was unknown for 8 pregnancies, they were excluded from survival analyses, leaving 99 evaluable patients in the ART group. At a median follow-up from conception of 5.2 years (IQR 2.2–9.2 years), 13 (3.45 per 100 person-years) and 118 (5.35 per 100 person-years) DFS events were observed in the ART and no-ART groups, respectively. The type of DFS, BCSS and OS events per 100 person-years in both groups are listed in Supplementary Table S1.

Compared to *BRCA1/2* carriers in the no-ART group, no apparent detrimental effect on DFS was observed in patients in the ART group (unadjusted HR=0.71, 95 % CI 0.41–1.21, $p = 0.206$; adjusted HR=0.72, 95 % CI 0.39–1.34, $p = 0.305$) (Figure 2).

In the secondary analysis according to type of ART procedure used to achieve a pregnancy (Supplementary Table S2), patients who conceived using oocyte donation were the oldest at diagnosis (median age 34 years) and at conception (median age 39.5 years) compared with those who conceived with oocyte/embryo cryopreserved at diagnosis (32 and 35.9 years, respectively) and those who underwent COS or ovulation induction after anticancer treatments (31 and 36.2 years, respectively). There were no differences among the three ART groups regarding

Table 2
Reproductive outcomes following breast cancer treatments.

	ART group n = 107	No-ART group n = 436	P-value
Median age at conception, y (IQR)	37.1 (34.1–39.5)	34.3 (31.4–36.5)	<0.001
Median time from breast cancer diagnosis to conception, y (IQR)	4.2 (2.9–6.1)	3.3 (2.0–4.9)	0.004
Pregnancy outcome, n (%)	n = 106	n = 431	0.015
-Live births	88 (83.0)	344 (79.8)	
-Ongoing pregnancies	5 (4.7)	13 (3.0)	
-Miscarriages	12 (11.3)	38 (8.8)	
-Induced abortions	1 (0.9)	36 (8.3)	
-Missing, n	1	5	
Timing of delivery,[e] n (%)	n = 76	n = 305	0.130
-At term (≥37 weeks)	65 (85.5)	279 (91.5)	
-Preterm (<37 weeks)	11 (14.5)	26 (8.5)	
-Missing, n	12	39	
Complications,[e] n (%)	n = 76	n = 292	0.220
-None	62 (81.6)	254 (87.0)	
-Pregnancy complications	9 (11.8)	16 (5.5)	
-Delivery complications	3 (4.0)	16 (5.5)	
-Fetal complications	1 (1.3)	2 (0.7)	
-Congenital abnormalities	0 (0.0)	3 (1.0)	
-Other complications	1 (1.3)	1 (0.3)	
-Missing, n	12	52	
Breast feeding,[e] n (%)	n = 75	n = 278	0.165
-No	56 (74.7)	182 (65.5)	
-Yes	19 (25.3)	96 (34.5)	
-Missing, n	13	66	
-Median duration, months (IQR)	5 (1–9)	4 (2–6)	
Type of ART, n (%)	n = 99	N/A	N/A
-COS for oocyte/embryo cryopreservation **at diagnosis**	45 (45.5)		
-COS for IVF/ICSI or ovulation induction for intrauterine insemination or planned intercourse **after anticancer treatments**[f]	33 (33.3)		
-**Oocyte donation**	21 (21.2)		
-**Unknown** type of ART	8		

Abbreviations: ART, assisted reproductive technology; COS; controlled ovarian stimulation; IQR, interquartile range; IVF, *In-vitro-fertilisation*; ICSI, intracytoplasmic sperm injection; y, years.

[e] Calculated among the patients with completed pregnancy.

[f] The number of patients who underwent ovulation induction for intrauterine insemination or planned intercourse after anticancer treatment was 2 out of 33.

pregnancy outcomes, timing of delivery and pregnancy complications (Supplementary Table S3). The type of DFS event according to the type of procedure used to achieve pregnancy, as well as BCSS and OS per 100 person-years, are listed in Supplementary Table S4. Compared to *BRCA1/2* carriers in the no-ART group, no apparent detrimental effect was observed on DFS according to the type of ART procedure (Supplementary Figure S1; Supplementary Table S5).

4. Discussion

This international hospital-based study investigated the safety of ART to achieve a pregnancy after breast cancer in young *BRCA1/2* carriers. Overall, compared with patients who conceived spontaneously, those in the ART group were older, more likely to be childless at breast cancer diagnosis and to have hormone receptor-positive tumours. They also had a longer median time between breast cancer diagnosis and conception than patients in the no-ART group. ART to achieve a pregnancy after breast cancer did not appear to be associated with worse DFS in young *BRCA1/2* carriers.

To date, the clinical evidence on the oncological safety of ART in patients with breast cancer harbouring germline *BRCA1/2* PVs is very limited. In the study by Derks-Smeets and colleagues, six young *BRCA1/2* carriers with breast cancer who underwent ART were included (three had their oocytes cryopreserved at diagnosis while three underwent COS after anticancer treatments) [15]. One case of cancer recurrence 2 months after COS performed following completion of anticancer treatments was described [15]. The study by Condorelli and colleagues, included 168 young *BRCA1/2* carriers with breast cancer with a pregnancy, 22 of which were achieved through ART. The small number of patients in the ART group did not allow for statistical comparisons [14].

Consistent with previous studies [11], baseline patient characteristics showed that women in the ART group were significantly older at the time of conception and had a longer time frame from diagnosis to conception as compared to those in the no-ART group. In the ART group, more patients had hormone-positive breast cancer; this result may be due to the indication to further delay conception during the 5–10 years of recommended adjuvant endocrine therapy [26,27]. For selected patients with hormone receptor-positive early breast cancer, the recent results of the POSITIVE trial have shown that a temporary interruption of endocrine therapy to attempt pregnancy can be considered safe after a median follow-up of 41 months [28]. A total of 38 *BRCA1/2* carriers were included in the study. Notably, with the limited 2-year window of treatment interruption allowed in the trial, 74 % achieved at least one pregnancy; among them, 43 % performed ART [29].

An advanced maternal age (usually defined as ≥35 years) is in itself a risk factor for infertility, and decreased of natural fertility with ageing is associated with an increased risk of miscarriages [30]. In our study, a slightly higher incidence of miscarriages among patients in the ART group was observed compared to the no-ART group (11.3 % vs. 8.8 %, respectively). These results may reflect the older median age at the time of pregnancy in the ART group. The opposite was observed for induced abortions (0.9 % vs. 8.3 %, respectively). Knowing the suboptimal use of contraception in young women with breast cancer [31,32], some patients who conceived spontaneously might have experienced an unintended pregnancy and then opted for an induced abortion.

In the ART group, most pregnancies were achieved with oocyte/embryo cryopreserved at diagnosis (45.5 %). According to a recent meta-analysis, COS for fertility preservation at diagnosis is safe in patients with breast cancer including those with hormone receptor-positive disease [12]. Similar reassuring results were observed in the two small studies that included *BRCA1/2* carriers [33,34].

Notably, in patients who completed anticancer therapies and did not undergo fertility preservation strategies at diagnosis, limited data are available on the oncological safety of ART [12,29], particularly in *BRCA1/2* carriers [14]. Our results did not show any signal for a detrimental effect on the oncological outcomes of using ART in patients who conceived after completion of anticancer therapy. However, these results must be interpreted with caution considering the very small number of included patients.

The major limitation of our study is the retrospective nature and the relatively small number of patients included in the ART group. As data were collected from oncological medical records or interviews with patients, there might be some imprecisions, missing data/misclassification and we cannot exclude unmeasured confounders. No information on use of preimplantation genetic testing for monogenic diseases (PGT-M) was collected. In addition, our results cannot be extrapolated to patients who used ART at diagnosis but did not conceive following treatment completion as data on ART use was only collected for patients who had a pregnancy after breast cancer. However, it should be highlighted that this is the largest study including young *BRCA1/2* carriers with breast cancer and it has a global representation.

Overall, our results add novel and specific information for the oncofertility counselling of young *BRCA1/2* carriers with a pregnancy after breast cancer. Most women achieved spontaneous pregnancies. Those who underwent ART to achieve a pregnancy had favourable oncological characteristics (52.9 % had tumour size ≤2 cm, 66.3 % node-negative disease, and 43.4 % hormone-positive malignancies). Hence, a multidisciplinary approach remains prerequisite to counsel young patients with breast cancer harbouring germline *BRCA1/2* PVs who are interested in ART. Oncofertility counselling should be routinely

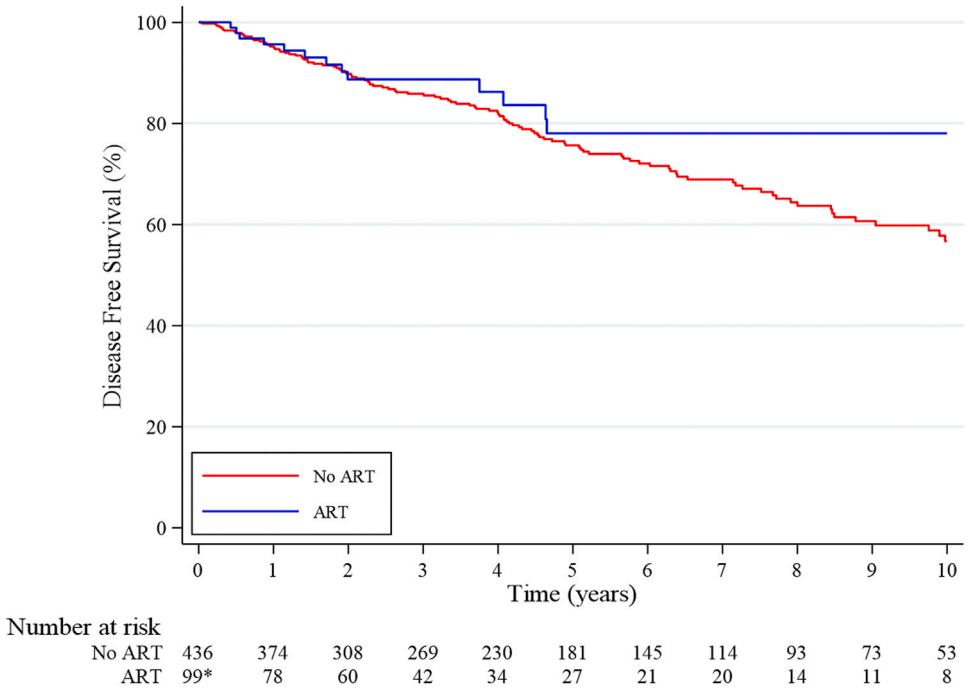

Fig. 2. Disease-free survival (DFS) in the ART group and no-ART group. Legend: 99 * : from the ART group of 107 women, 8 were excluded from the analysis because the type of ART was unknown. Legend abbreviations: ART, assisted reproductive technology; DFS, disease-free survival.

offered as soon as possible before starting treatment to young patients with breast cancer [1]. This is especially crucial for *BRCA1/2* carriers in view of the potentially increased risk of chemotherapy-induced premature ovarian insufficiency, their possible interest in PGT-M [35], and the indication to risk reducing bilateral salpingo-oophorectomy at a young age [1,36].

5. Conclusion

Our study showed that the use of ART to achieve a pregnancy after breast cancer in young *BRCA1/2* carriers did not appear to be associated with increased risk of DFS events or worse pregnancy outcomes. Given the interest of many women in avoiding the transmission of the germline *BRCA1/2* PV by PGT-M [37], our results may help to improve the oncofertility counselling of these patients. Future prospective studies are needed to confirm our results.

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CRediT authorship contribution statement

Isotta Martha Magaton: Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Eva Blondeaux:** Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing. **Anne-Sophie Hamy:** Validation, Writing – review & editing. **Sabine Linn:** Validation, Writing – review & editing. **Rinat Bernstein-Molho:** Writing – review & editing. **Fedro A. Peccatori:** Writing – review & editing. **Alberta Ferrari:** Writing – review & editing. **Estela Carrasco:** Writing – review & editing. **Shani Paluch-Shimon:** Writing – review & editing. **Elisa Agostinetto:** Writing – review & editing. **Marta Venturelli:** Writing – review & editing. **Ines Maria Vaz Luis:** Writing – review & editing. **Kenny A. Rodriguez-Wallberg:** Writing – review & editing. **Hee Jeong Kim:** Writing – review & editing. **Kimia Sorouri:** Writing – review & editing. **Tiphaine Renaud:** Writing – review & editing. **Halle C.F. Moore:** Writing – review & editing. **Wanda Cui:** Writing – review & editing. **Jyoti Bajpa:** Writing – review & editing. **Christine Rousset-Jablonski:** Writing – review & editing. **Laura De Marchis:** Writing – review & editing. **Rinat Yerushalmi:** Writing – review & editing. **Stephanie M. Wong:** Writing – review & editing. **Sileny Han:** Writing – review & editing. **Kelly-Anne Phillips:** Writing – review & editing. **Katarzyna Pogoda:** Writing – review & editing. **Fabio Puglisi:** Writing – review & editing. **Alessandra Chirco:** Writing – review & editing. **Francois P. Duhoux:** Writing – review & editing. **Icro Meattini:** Writing – review & editing. **Cynthia Villarreal-Garza:** Writing – review & editing. **Claudio Vernieri:** Writing – review & editing. **Marco Bruzzone:** Data curation, Formal analysis, Writing – review & editing. **Isabelle Demeestere:** Writing – review & editing. **Hatem A. Azim:** Writing – review & editing. **Ann H. Partridge:** Writing – review & editing. **Matteo Lambertini:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

E. Blondeaux reports speaking honoraria from Eli Lilly and research grant to the institution from Gilead, all outside the submitted work.

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A. Ferrari reports speaking fee/honoraria from AstraZeneca and MSD. All outside the submitted work.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115434.

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