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ORIGINAL ARTICLE

# Reproductive potential and performance of fertility preservation strategies in *BRCA*-mutated breast cancer patients

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**Background:** Preclinical evidence suggests a possible negative impact of deleterious *BRCA* mutations on female fertility. However, limited and rather conflicting clinical data are available. This study assessed the reproductive potential and performance of fertility preservation strategies in *BRCA*-mutated breast cancer patients.

**Patients and methods:** This was a retrospective analysis of two prospective studies investigating oocyte cryopreservation and ovarian tissue cryopreservation in newly diagnosed early breast cancer patients. In the current analysis, baseline anti-Mullerian hormone (AMH) and performance of cryopreservation strategies were compared between patients with or without germline deleterious *BRCA* mutations.

**Results:** Out of 156 patients included, 101 had known *BRCA* status of whom 29 (18.6%) were *BRCA*-mutated and 72 (46.1%) had no mutation. Median age in the entire cohort was 31 years [interquartile range (IQR) 28–33). Median AMH levels were 1.8 μg/l (IQR 1.0–2.7) and 2.6 μg/l (IQR 1.5–4.1) in the *BRCA*-positive and *BRCA*-negative cohorts, respectively ($P = 0.109$). Among patients who underwent oocyte cryopreservation ($N = 29$), women in the *BRCA*-positive cohort tended to retrieve (6.5 versus 9; $P = 0.145$) and to cryopreserve (3.5 versus 6; $P = 0.121$) less oocytes than those in the *BRCA*-negative cohort. Poor response rate (i.e. retrieval of ≤4 oocytes) was 40.0% and 11.1% in the *BRCA*-positive and *BRCA*-negative cohorts, respectively ($P = 0.147$). Among patients who underwent ovarian tissue cryopreservation ($N = 72$), women in the *BRCA*-positive cohort tended to have a numerically lower number of oocytes per fragment (0.08 versus 0.14; $P = 0.193$) and per square millimeter (0.33 versus 0.78; $P = 0.153$) than those in the *BRCA*-negative cohort. Two *BRCA*-mutated patients were transplanted after chemotherapy and one delivered at term a healthy baby. No difference between *BRCA1*- and *BRCA2*-mutated patients was observed in any of the above-mentioned outcomes.

**Conclusion:** A consistent trend for reduced reproductive potential and performance of cryopreservation strategies was observed in *BRCA*-mutated breast cancer patients. Independent validation of these results is needed.

**Key words:** *BRCA1/2*, fertility, breast cancer, anti-Mullerian hormone, oocyte cryopreservation, ovarian tissue cryopreservation

## Introduction

Over the past years, major advances in oncology practice have led to significant survival improvements in breast cancer patients including those diagnosed at a young age. Therefore, survivorship issues are of crucial importance to be taken into account when managing these patients [1]. Anticancer treatments in young women with breast cancer can be associated with the added burden of potential premature ovarian failure (POF) and subsequent infertility [2]. As recently indicated by young women advocates, fertility preservation is a priority area of concern for

these patients [1]. Therefore, oncofertility counseling to discuss POF risk and the available fertility preservation options should be considered standard of care in all newly diagnosed young breast cancer patients [1, 3].

Up to 8% of the cases diagnosed in young breast cancer patients are hereditary tumors related to germline deleterious mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2*; the cumulative breast cancer risk at 40 years of age is approximately 24% for *BRCA1* carriers and 13% for *BRCA2* carriers [4]. Carrying a deleterious *BRCA* mutation plays a relevant role in cancer prevention, diagnosis and treatment; furthermore, it has been suggested to negatively impact the reproductive potential of these women [5]. However, limited and rather conflicting clinical data are available to support this hypothesis.

In recent years, the role of fertility preservation strategies (such as cryopreservation of oocytes/embryos and ovarian tissue) has become more established and they are currently widely adopted in young breast cancer patients [2]. Nevertheless, to date, limited evidence exists on the reproductive potential and performance of fertility preservation strategies in *BRCA*-mutated breast cancer patients [5]. In addition, *BRCA* carriers face unique issues including the consideration for prophylactic gynecological surgery at a young age and the possible interest in preimplantation genetic diagnosis. Therefore, in this patient population, oncofertility counseling is particularly complex. To acquire more insights on this unmet medical issue, we conducted the present study to evaluate the reproductive potential and performance of cryopreservation procedures in *BRCA*-mutated breast cancer patients.

## Methods

### Study design and participants

This is a retrospective analysis conducted within two prospective studies that involved young women with newly diagnosed breast cancer who underwent oocyte cryopreservation [6] or ovarian tissue cryopreservation [7] for fertility preservation at CUB-Hôpital Erasme in Brussels (Belgium). Eligible patients were premenopausal women with no history of gonadotoxic treatments, no contraindications to surgical procedures and diagnosis of early breast cancer at a young age ($\leq$40 years for oocyte cryopreservation and $\leq$35 years for ovarian tissue cryopreservation). All patients who underwent oocyte cryopreservation received a gonadotropin-releasing hormone (GnRH) antagonist protocol for controlled ovarian stimulation associated with letrozole (5 mg/d) administered throughout the cycle until the day of ovulation trigger [6].

All patients were subjected to oncofertility counseling for accessing cryopreservation procedures shortly after breast cancer diagnosis. Genetic susceptibility to breast cancer was known only in two patients at the time of oncofertility counseling; for the others, genetic testing was requested by the treating oncologists and became available at different time points during follow-up. Therefore, genetic susceptibility did not influence oncofertility counseling for the type of cryopreservation procedure offered.

For the purpose of the present analysis, patients were divided into four cohorts: women with deleterious *BRCA1* or *BRCA2* mutations (*BRCA*-positive cohort), those without *BRCA* mutations (*BRCA*-negative cohort), patients who did not undergo any genetic test (*BRCA*-untested cohort) and those who underwent a genetic test but had *BRCA* mutations classified as variant of unknown significance or germline mutations other than *BRCA* (other-mutation cohort).

The current analysis was approved by the ethics committee and written informed consent was obtained from all patients before study inclusion.

### Study objectives

The main objectives of the present analysis were to compare the reproductive potential and performance of cryopreservation procedures between breast cancer patients with or without *BRCA* mutations. Patients' reproductive potential was assessed at the time of oncofertility counseling (i.e. before starting anticancer treatment) by evaluating anti-Mullerian hormone (AMH) levels. AMH was centrally performed at CUB-Hôpital Erasme. The performance of fertility preservation strategies was assessed by evaluating oocyte yield, cryopreserved oocytes and poor response rate (defined as retrieval of $\leq$4 oocytes) in case of oocyte cryopreservation, and number of oocytes per fragment and number of oocytes per square millimeter in case of ovarian tissue cryopreservation.

Preplanned subgroup analyses aimed at investigating potential differences in the reproductive potential and performance of cryopreservation procedures between *BRCA1*- and *BRCA2*-mutated patients.

### Statistical analysis

All statistical comparisons were performed between the *BRCA*-positive and *BRCA*-negative cohorts with further descriptive details provided for *BRCA1*- and *BRCA2*-mutated subgroups. The reproductive potential and performance of cryopreservation procedures in the *BRCA*-untested and the other-mutation cohorts were described to provide further context of fertility parameters in breast cancer patients (supplementary Tables S1–S3 and Figure S1, available at *Annals of Oncology* online).

Baseline characteristics were tabulated according to *BRCA* status and differences tested using chi-squared test, Fisher exact test or Wilcoxon–Mann–Whitney test, as appropriate. To compare between characteristics of fertility preservation strategies and their outcomes according to *BRCA* status, chi-square test, Fisher exact test or Wilcoxon–Mann–Whitney test were used, as appropriate. A logistic regression analysis was performed to investigate the association between *BRCA*-mutated status and poor response to controlled ovarian stimulation. Missing information was considered missing completely at random.

All reported *P* values were two-sided, with values less than 0.05 considered as statistically significant. Statistical analyses were performed using Stata 13.1 (StataCorp LP).

## Results

Between January 2006 and December 2016, out of 159 breast cancer patients enrolled in the two prospective studies, 156 were included in the present analysis (supplementary Figure S2, available at *Annals of Oncology* online). A total of 29 (18.6%) patients had germline deleterious *BRCA* mutations (19 with *BRCA1* and 10 with *BRCA2* mutations) and 72 (46.1%) had no mutations.

Median age in the entire cohort was 31 years [interquartile range (IQR) 28–33] with no difference between the *BRCA*-positive and *BRCA*-negative cohorts. Baseline characteristics were similar between the two cohorts with the exception of higher mastectomy rate (53.6% versus 32.4%, $P = 0.034$), lower incidence of hormone receptor–positive (24.1% versus 65.3%, $P < 0.001$) and HER2-positive (6.9% versus 33.8%, $P = 0.005$) tumors in the *BRCA*-positive cohort (supplementary Table S4, available at *Annals of Oncology* online).

At the time of oncofertility counseling, AMH was tested in 85 patients (supplementary Figure S2, available at *Annals of Oncology* online). AMH levels were strongly correlated with patients' age (supplementary Figure S3, available at *Annals of*

*Oncology* online). Median AMH levels were 1.8 μg/l (IQR, 1.0–2.7) and 2.6 μg/l (IQR, 1.5–4.1) in the *BRCA*-positive and *BRCA*-negative cohorts, respectively ($P = 0.109$; Figure 1A). A total of 8 (32.0%) and 12 (20.0%) patients had AMH levels ≤1 μg/l in the *BRCA*-positive and *BRCA*-negative cohorts, respectively ($P = 0.235$). No difference was observed between *BRCA1*- and *BRCA2*-mutated patients (Figure 1B).

A total of 29 patients underwent oocyte cryopreservation (supplementary Figure S2, available at *Annals of Oncology* online). Patients in the *BRCA*-positive cohort received a numerically higher dose of gonadotropins (2775 versus 2025 IU; $P = 0.085$) and longer duration of stimulation (11.5 versus 9 days; $P = 0.110$), yet they tended to retrieve (6.5 versus 9; $P = 0.145$) and to cryopreserve (3.5 versus 6; $P = 0.121$) less oocytes than those in the *BRCA*-negative cohort (Table 1). Poor response rate was 40.0% and 11.1% in the *BRCA*-positive and *BRCA*-negative cohorts, respectively ($P = 0.147$). The odds ratio for poor response was 5.3 (95% confidence intervals 0.8–37.1; $P = 0.091$). No difference in maturation rate was observed between the two cohorts (0.8 versus 0.9; $P = 0.888$). *BRCA1*- and *BRCA2*-mutated patients showed similar outcomes (Table 1). To date, none of the patients who underwent oocyte cryopreservation have returned for pursuing embryo transfer.

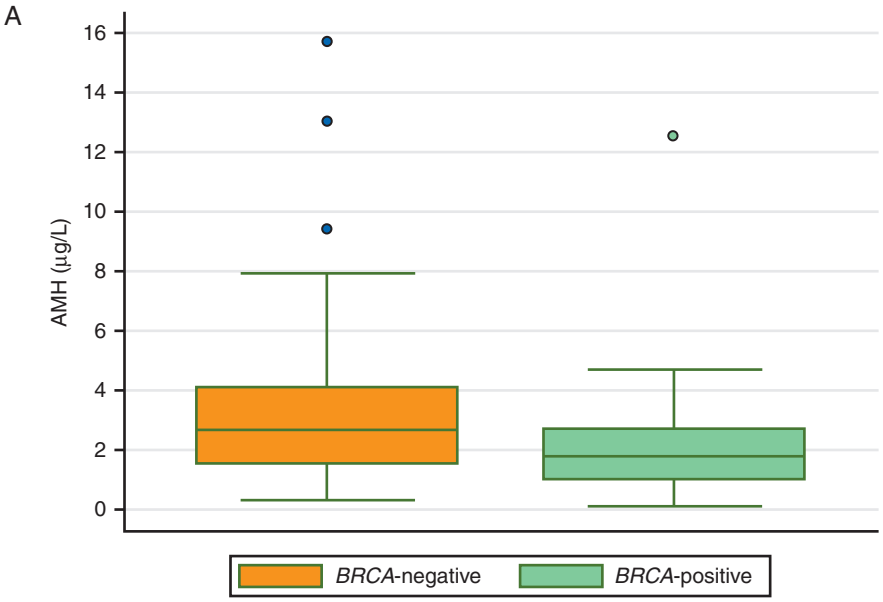
A total of 72 patients underwent ovarian tissue cryopreservation (supplementary Figure S2, available at *Annals of Oncology* online). In more than 84% of the cases, bilateral ovarian tissue fragments were collected. Immature oocytes were collected *ex vivo* from ovarian tissue fragments before cryopreservation [7]. Patients in the *BRCA*-positive cohort tended to have a numerically lower number of oocytes per fragment (0.08 versus 0.14; $P = 0.193$) and per square millimeter (0.33 versus 0.78; $P = 0.153$) than those in the *BRCA*-negative cohort (Table 2). Two patients were transplanted after chemotherapy. The first patient was diagnosed at the age of 30 years and has a *BRCA1* mutation. She was transplanted with 8 out of 17 cryopreserved fragments of ovarian tissue grafted to the remaining ovaries 69 months after chemotherapy. After preimplantation genetic diagnosis showing that the embryo carried the mutation, the patient decided not to proceed further with conception projects. The second patient was diagnosed at the age of 33 and has a *BRCA2* mutation. She was transplanted with 8 out of 13 cryopreserved fragments of ovarian tissue grafted to the remaining ovaries 55 months after chemotherapy completion. Five months after transplantation, she had recovery of ovarian function followed 3 months later by a spontaneous pregnancy. After an uneventful pregnancy, the patient delivered vaginally without complications a healthy boy at term weighing 4000 g.

## Discussion

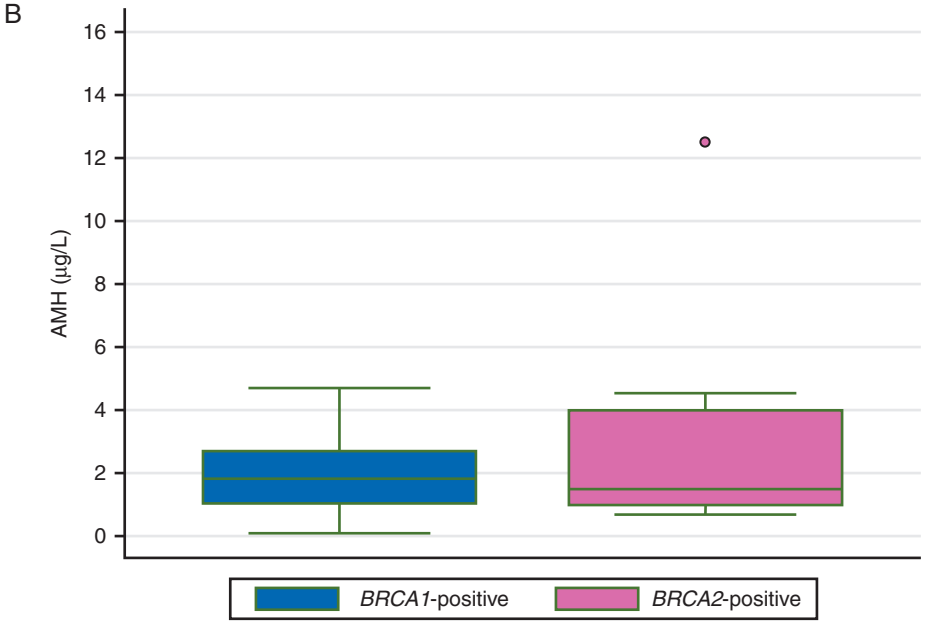
To our knowledge, this is the largest comprehensive analysis investigating fertility parameters in *BRCA*-mutated breast cancer patients. We observed a consistent trend for reduced reproductive potential and performance of both oocyte and ovarian tissue cryopreservation in the *BRCA*-positive cohort. These findings, that need to be confirmed in larger *ad hoc* studies, should be taken into account and may influence the oncofertility counseling of this specific patient population.

The *BRCA* genes seem to be implicated in gametogenesis; as shown in animal experiments, mice harboring *BRCA* mutations may have a lower ovarian reserve and their oocytes a higher frequency of nuclear abnormalities [8]. *BRCA* mutations lead to impaired DNA double-strand breaks (DSBs) repair mechanism. This can be associated with decreased possibility to counteract genotoxic stress and subsequent potential accelerated loss of ovarian reserve following the accumulation of DSBs in the oocytes [8]. Nevertheless, despite a strong biologic rationale supported by preclinical data, limited clinical evidence exists on the possible impact of carrying a *BRCA* mutation on female reproductive potential [5]. The only other study available that investigated this issue in breast cancer patients showed significantly lower AMH levels (1.22 versus 2.23 ng/ml; $P < 0.001$) in *BRCA* carriers [9]. Similarly, we observed a trend for lower median AMH value in the *BRCA*-positive cohort (1.8 versus 2.6 μg/l; $P = 0.109$). In the study by Titus and colleagues, *BRCA1*-mutated patients seemed to have lower AMH levels than *BRCA2* carriers (1.12 versus 1.39 ng/ml) [9]; on the contrary, no difference was observed in our study within the *BRCA*-positive cohort (1.8 versus 1.5 μg/l). As recently shown in healthy *BRCA* carriers [10], a possible negative impact of *BRCA2* mutations on reproductive potential may be also present; nevertheless, this can be less apparent due to the delayed decline of the normal *BRCA2* allele function.

Embryo/oocyte cryopreservation is the first option for fertility preservation to be discussed with breast cancer patients [1, 3]. Of note, this strategy would also allow to access preimplantation genetic diagnosis. Due to the potential increased risk of fertility-related problems in this specific population, it has been suggested that *BRCA*-mutated breast cancer patients may have a lower response to controlled ovarian stimulation. Two single-institution studies including a total of 32 *BRCA*-mutated patients have investigated this issue. In the Israeli study, no difference in terms of oocytes collected (11.50 versus 11.69; $P = 0.92$) was observed between *BRCA*-positive and *BRCA*-negative breast cancer patients, respectively [11]. Different protocols for controlled ovarian stimulation were used in this study and tamoxifen was coadministered in 19% of the *BRCA* carriers [11]. In the American study, all patients received a GnRH-antagonist protocol with the use of letrozole [12]. As compared to the *BRCA*-negative cohort, a lower number of collected oocytes (7.9 versus 11.3; $P = 0.025$) and higher poor response rate (33.3% versus 3.3%; $P = 0.014$) was observed in the *BRCA*-positive cohort. The low performance of controlled ovarian stimulation was mainly observed in *BRCA1*-mutated patients [12]. Similarly, in our study, after controlled ovarian stimulation with a GnRH-antagonist protocol that included letrozole, patients in the *BRCA*-positive cohort tended to retrieve less oocytes (6.5 versus 9.0; $P = 0.145$) and to have a higher poor response rate (40.0% versus 11.1%; $P = 0.147$) than those in the *BRCA*-negative cohort. A similar performance in *BRCA1*- and *BRCA2*-mutated patients was observed. Importantly, our study showed that the meiotic maturation competence of the oocytes was comparable between the *BRCA*-positive and *BRCA*-negative cohorts (0.8 versus 0.9; $P = 0.888$); this suggests that the potential accelerated ovarian aging in *BRCA*-mutated patients [9] may still not be evident in young women. Acknowledging the limited data available on the topic, although a negative impact of *BRCA* mutations on the performance of controlled ovarian stimulation cannot be




| | *BRCA*-negative cohort (*N*=60) | *BRCA*-positive cohort (*N*=25) | *P* values |
|---|---|---|---|
| Anti-Mullerian hormone levels, median (IQR) | 2.6 (1.5-4.1) | 1.8 (1.0-2.7) | 0.109 |
| Anti-Mullerian hormone levels, *N* (%)<br>≤ 1.0<br>> 1.0 | <br>12 (20.0)<br>48 (80.0) | <br>8 (32.0)<br>17 (68.0) | 0.235 |




| | *BRCA1*-positive (*N*=15) | *BRCA2*-positive (*N*=10) | *P* values |
|---|---|---|---|
| Anti-Mullerian hormone levels, median (IQR) | 1.8 (1.0-2.7) | 1.5 (0.9-4.0) | 0.934 |
| Anti-Mullerian hormone levels, *N* (%)<br>≤ 1.0<br>> 1.0 | <br>4 (26.7)<br>11 (73.3) | <br>4 (40.0)<br>6 (60.0) | 0.667 |

**Figure 1.** AMH levels (A) in the *BRCA*-positive and the *BRCA*-negative cohorts, and (B) in *BRCA1*- and *BRCA2*-mutated patients. AMH, anti-mullerian hormone; IQR, interquartile range.

**Table 1. Oocyte cryopreservation in the BRCA-positive and BRCA-negative cohorts**

| | *BRCA*-positive cohort (*N* = 10, 34.5%) | | | *BRCA*-negative cohort (*N* = 19, 65.5%) | *P* values[a] (*BRCA*-positive versus *BRCA*-negative) |
|---|---|---|---|---|---|
| | *BRCA1*-positive (*N* = 5, 50.0%) | *BRCA2*-positive (*N* = 5, 50.0%) | *BRCA*-positive cohort (*N* = 10, 100%) | | |
| Total FSH dose (IU), median (IQR) | 2775 (2700–2850) | 2775 (1800–3000) | 2775 (1800–3000) | 2025 (1575–2425) | 0.085 |
| Type of stimulation, *N* (%) | | | | | |
| Follicular | 3 (60.0) | 3 (60.0) | 6 (60.0) | 11 (57.9) | 1.000 |
| Random | 2 (40.0) | 2 (40.0) | 4 (40.0) | 8 (42.1) | |
| Stimulation days, median (IQR) | 11 (10–11) | 12 (12–12) | 11.5 (10–12) | 9 (8–11) | 0.110 |
| E2 at trigger (pmol/l), median (IQR) | 419 (95–442) | 187 (159–238) | 213 (95–442) | 200 (92–615) | 0.909 |
| P at trigger (pmol/l), median (IQR) | 1.37 (0.81–1.76) | 0.45 (0.45–1.50) | 1.09 (0.45–1.76) | 0.84 (0.59–1.40) | 0.854 |
| Number of oocytes, median (IQR) | 7 (3–7) | 6 (3–7) | 6.5 (3–7) | 9 (5–13) | 0.145 |
| Number of mature oocytes, median (IQR) | 7 (3–7) | 4 (2–5) | 4.5 (2–7) | 7 (5–9) | 0.299 |
| Maturation rate, median (IQR) | 1.0 (1.0–1.0) | 0.7 (0.7–0.7) | 0.8 (0.7–1.0) | 0.9 (0.7–1.0) | 0.888 |
| Number of cryopreserved oocytes, median (IQR) | 5 (2–7) | 3 (2–4) | 3.5 (2–7) | 6 (4–12) | 0.121 |
| Poor response rate, *N* (%) | 2 (40.0) | 2 (40.0) | 4 (40.0) | 2 (11.1) | 0.147 |

[a]Calculated excluding the unknown values.
FSH, follicle-stimulating hormone; IQR, interquartile range; E2, estradiol; P, progesterone.

**Table 2. Ovarian tissue cryopreservation in the BRCA-positive and BRCA-negative cohorts**

| | *BRCA*-positive cohort (*N* = 19, 26.4%) | | | *BRCA*-negative cohort (*N* = 53, 73.6%) | *P* values[a] (*BRCA*-positive versus *BRCA*-negative) |
|---|---|---|---|---|---|
| | *BRCA1*-positive (*N* = 14, 73.7%) | *BRCA2*-positive (*N* = 5, 26.3%) | *BRCA*-positive cohort (*N* = 19, 100%) | | |
| Type of surgery, *N* (%) | | | | | |
| Unilateral | 3 (21.4) | 0 (0.0) | 3 (15.8) | 4 (7.6) | 0.371 |
| Bilateral | 11 (78.6) | 5 (100) | 16 (84.2) | 49 (92.4) | |
| Fragments, median (IQR) | 17 (13–20) | 25 (20–28) | 17 (13–23) | 18 (14–22) | 0.913 |
| Follicle density[b], median (IQR) | 5 (3–6) | 4 (3–12) | 4.5 (3–7) | 6 (4–10) | 0.318 |
| Not evaluated, *N* (%) | 1 (7.1) | 0 (0.0) | 1 (5.3) | 3 (5.7) | |
| Number of oocytes, median (IQR) | 3 (0–8) | 1 (0–3) | 2 (0–8) | 2 (1–6) | 0.682 |
| Not collected, *N* (%) | 7 (50) | 0 (0.0) | 7 (36.8) | 18 (34.0) | |
| Number of oocytes per fragment, median (IQR) | 0.08 (0–0.24) | 0.08 (0.03–0.20) | 0.08 (0–0.24) | 0.14 (0.06–0.29) | 0.193 |
| Not evaluated, *N* (%) | 8 (57.1) | 1 (20.0) | 9 (47.4) | 28 (52.8) | |
| Number of oocytes per $mm^2$, median (IQR) | 0.24 (0–1.10) | 0.37 (0.90–0.78) | 0.33 (0–1.00) | 0.78 (0.20–1.20) | 0.153 |
| Not evaluated, *N* (%) | 8 (57.1) | 1 (20.0) | 9 (47.4) | 28 (52.8) | |
| Number of cryopreserved oocytes, median (IQR) | 1 (0–1) | 1 (0–2) | 1 (0–1) | 0 (0–1) | 0.422 |
| Not collected, *N* (%) | 7 (50.0) | 0 (0.0) | 7 (36.8) | 18 (34.0) | |

[a]Calculated excluding the unknown values.
[b]Number of follicles per $mm^2$.
IQR, interquartile range.

excluded, our study confirmed that embryo/oocyte cryopreservation is feasible and remains the first fertility preservation option to be discussed also in *BRCA*-mutated breast cancer patients. Appropriate counseling is particularly important in these patients as the chemotherapy-induced ovarian damage might be also more pronounced [5].

Although still experimental, ovarian tissue cryopreservation is an effective technique for fertility preservation that may be proposed to selected breast cancer patients such as those who cannot delay anticancer treatments or with contraindications to controlled ovarian stimulation [2]. Our study including 19 *BRCA*-mutated breast cancer patients is the largest series reporting the

performance of ovarian tissue cryopreservation in this setting. The lower number of oocytes per fragment (0.08 versus 0.14; $P = 0.193$) and per square millimeter (0.33 versus 0.78; $P = 0.153$) observed in the *BRCA*-positive cohort are in line with the other findings from our study suggesting a possible reduced reproductive potential in these patients. However, the procedure can be successful also in this setting with one out of two transplanted patients who had a live birth. This is the second baby described after ovarian tissue transplantation in *BRCA*-mutated breast cancer patients [13]. Due to the risk of developing ovarian cancer, prophylactic bilateral salpingo-oophorectomy before the age of 40 years is generally recommended in *BRCA* carriers [14]. Hence, ovarian tissue cryopreservation is not an optimal technique in this setting. However, for most of the patients, *BRCA* status is not available at the time of oncofertility counseling. In patients who undergo ovarian tissue cryopreservation at breast cancer diagnosis and consider to proceed to transplantation after the end of treatment, a genetic test should be requested. In women found to be *BRCA*-mutated and who are younger than the recommended age for prophylactic bilateral salpingo-oophorectomy, the procedure can be feasible as suggested by our study. In this specific setting, it is recommended to transplant the ovarian tissue only to the remaining ovaries so that the gonads can be removed after the completion of reproductive plans. From an ethical perspective, it remains controversial how to deal with frozen ovarian tissue collected from patients found to be *BRCA*-mutated and who are close to the recommended age for prophylactic bilateral salpingo-oophorectomy. In the future, a potential approach in this setting may be represented by *in vitro* growth of isolated immature ovarian follicles without the need to undergo ovarian tissue transplantation [5]. However, further research efforts are needed on this regard.

Some limitations should be considered in the interpretation of our results. This is a retrospective analysis conducted in a relatively small population. Nevertheless, it was performed within two prospective studies conducted in an institution with known expertise in the field, and this remains the largest comprehensive analysis available to date on this topic. Although all the results were in the same direction suggesting a possible negative impact of *BRCA* mutations on fertility parameters in line with biologic and preclinical evidence, no statistical significance was shown and thus no solid conclusions can be drawn. Nevertheless, this study raises awareness about the possible need of personalized approaches for young women with *BRCA*-mutated breast cancer who are interested in pursuing fertility preservation strategies before starting anticancer treatments.

In conclusion, our study showed that *BRCA*-mutated breast cancer patients may have a reduced reproductive potential; although feasible, fertility preservation procedures may be characterized by lower performance in this setting. Considering both that most of young women with breast cancer are nowadays candidates to undergo genetic testing and the widespread use of multi-gene panel sequencing technologies in germline risk assessment [15], a growing importance should be paid to fertility issues in patients with hereditary cancer syndromes. Further larger reproduction studies are needed to improve the oncofertility counseling and the success of the available fertility preservation options in this patient population.

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## Disclosure

ML served as a consultant for Teva and has received travel grants from Astellas outside the submitted work. HAA reports employment at Innate Pharma at the end of this study; this employment is not related in any sort to the subject of the current study. EdA has received honoraria from Roche, travel grants from Roche and GlaxoSmithKline, and research grant from Roche (to the Institution) outside the submitted work. MI served as a consultant for Roche and received research grant from Roche (to the Institution) outside the submitted work. All remaining authors have declared no conflicts of interest.

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