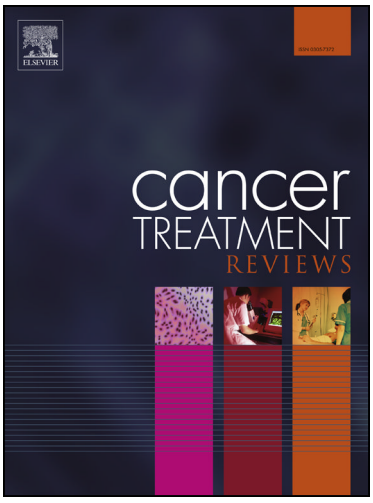


Complications of Treatment

# Fertility And Pregnancy Issues In *Brca*-Mutated Breast Cancer Patients

Matteo Lambertini, Oranite Goldrat, Angela Toss, Hatem A. Azim Jr., Fedro A. Peccatori, Michail Ignatiadis, Lucia Del Mastro, Isabelle Demeestere

PII: S0305-7372(17)30106-8
DOI: http://dx.doi.org/10.1016/j.ctrv.2017.07.001
Reference: YCTRV 1650

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 2 June 2017
Revised Date: 4 July 2017
Accepted Date: 5 July 2017

Please cite this article as: Lambertini, M., Goldrat, O., Toss, A., Azim, H.A. Jr., Peccatori, F.A., Ignatiadis, M., Del Mastro, L., Demeestere, I., Fertility And Pregnancy Issues In *Brca*-Mutated Breast Cancer Patients, *Cancer Treatment Reviews Cancer Treatment Reviews* (2017), doi: http://dx.doi.org/10.1016/j.ctrv.2017.07.001

# FERTILITY AND PREGNANCY ISSUES IN *BRCA*-MUTATED BREAST CANCER PATIENTS

Matteo Lambertini[1,2,*], Oranite Goldrat[3], Angela Toss[4], Hatem A. Azim Jr.[2], Fedro A. Peccatori[5], Michail Ignatiadis[2], Lucia Del Mastro[6], Isabelle Demeestere[3]

**Address**:

[1] Breast Cancer Translational Research Laboratory, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

[2] Department of Medical Oncology, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

[3] Fertility Clinic, Research Laboratory on Human Reproduction, CUB-Erasme, and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

[4] Department of Oncology and Hematology, University Hospital of Modena and Reggio Emilia, Modena, Italy

[5] Fertility and Procreation Unit, Gynecologic Oncology Department, European Institute of Oncology, Milan, Italy

[6] Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, IRCCS AOU San Martino-IST, Genova, Italy

[*]**Corresponding author:** Matteo Lambertini, MD

Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.)

Boulevard de Waterloo, 121, 1000 – Brussels (Belgium)

Telephone - +32 2 541 3099

E-mail: matteo.lambertini85@gmail.com

# FERTILITY AND PREGNANCY ISSUES IN *BRCA*-MUTATED BREAST CANCER PATIENTS


## ABSTRACT

Fertility and pregnancy-related issues represent one of the main areas of concerns for young women with breast cancer. Carrying a germline deleterious *BRCA* mutation adds additional burden on this regard due to the specific issues that should be considered during the oncofertility counseling of this special patient group. Despite the availability of a growing amount of data in the general breast cancer population on the feasibility and safety of fertility preservation and pregnancy after diagnosis, numerous challenges remain for *BRCA*-mutated breast cancer patients in whom very limited studies have been performed so far. Therefore, studies aiming to address the specific issues of these patients, including the impact of the mutation on their fertility potential, the safety and efficacy of the different strategies for fertility preservation, and the feasibility of having a pregnancy after diagnosis, should be considered a research priority.

The aim of the present manuscript is to perform an in depth overview on the role of *BRCA* mutations in breast cancer with a specific focus on their impact on reproductive potential, and to discuss the fertility and pregnancy issues faced by *BRCA*-mutated breast cancer patients. The final goal of this manuscript is to highlight current and upcoming knowledge in this field for trying to help physicians dealing with these patients during oncofertility counseling.

## HIGHLIGHTS

- Fertility and pregnancy-related issues are one of the main areas of concerns for young women with breast cancer.
- Carrying a germline deleterious *BRCA* mutation adds additional burden on this regard.
- Specific needs and issues should be considered when counseling *BRCA*-mutated breast cancer patients.
- Reproduction studies in *BRCA*-mutated breast cancer patients should be considered a research priority.

## KEYWORDS

Breast cancer; young women; *BRCA*; fertility; pregnancy.

**MANUSCRIPT**

## 1. Introduction

Breast cancer is the most frequent malignancy arising in women of reproductive age [1]. Thanks to major advances in oncology practice over the past years, young women with breast cancer have nowadays excellent survival rates [2]. Hence, the maintenance of a good long-term quality of life represents a crucial goal to be accomplished when managing these patients. Among the different side effects of anticancer treatments in this patient population, the possible development of premature ovarian failure (POF) and subsequent infertility are prevalent concerns that add significant anxiety and emotional strain during treatment decision-making [3]. Hence, all newly diagnosed young patients should be informed before starting anticancer treatment about the possible development of POF and infertility, and fertility preservation options should be discussed with interested patients [4–7].

Approximately 5-10% of breast cancer cases are related to hereditary conditions and, in more than 80% of hereditary breast tumors, the responsible genetic abnormality is a germline deleterious mutation in the breast cancer susceptibility genes *BRCA1* or *BRCA2* [8]. Harboring a deleterious *BRCA* mutation is associated with an increased lifetime risk of breast and ovarian cancer carcinogenesis, the so called hereditary breast and ovarian cancer syndrome [9]. Specifically, the average cumulative risk of breast cancer and ovarian cancer by 80 years of age is 67% and 45% for *BRCA1*-mutation carriers and 66% and 12% for *BRCA2*-mutation carriers, respectively, being higher in younger women and decreasing with aging [10]. In *BRCA*-mutation carriers, breast cancer often occurs during reproductive age, while ovarian cancer is very rare before the age of 40-45 years [10]. The identification of a deleterious *BRCA* mutation plays a relevant role in the management of hereditary cancer prevention, diagnosis and treatment, with subsequent impact also

on the reproductive potential of these women.

Over the past years, a growing attention has been given to maintenance of fertility and future reproductive potential in young women with breast cancer [11]. Despite the development of specific programs to support clinicians in the oncofertility counseling [12,13], there are still several barriers in discussing these issues with subsequent limited access to fertility preservation procedures and low percentage of breast cancer survivors who achieve a pregnancy [11]. This is even more challenging in young women with *BRCA* mutations. In fact, unique issues should be considered in *BRCA*-mutated breast cancer patients, such as the indication of prophylactic gynecological surgery at a young age, the impact of anticancer treatments on ovarian function with subsequent risk of developing POF, and the possible wish to eliminate the mutation from future offspring [14]. Hence, for all these reasons, the window for fertility and pregnancy may be particularly narrow in these young women [15].

The aim of the present manuscript is to perform an in depth overview on the role of *BRCA* mutations in breast cancer with a specific focus on their impact on reproductive potential, and to discuss the fertility and pregnancy issues faced by *BRCA*-mutated breast cancer patients. The final goal of this manuscript is to highlight current and upcoming knowledge in this field for trying to help physicians dealing with these patients during oncofertility counseling.

## 2. *BRCA* mutations and breast cancer

Thousands of different pathogenic mutations of *BRCA* genes have been identified and are classified in open access on-line mutation databases, such as the Breast Cancer Information Core and the *BRCA* Share™ (https://research.nhgri.nih.gov/bic/ - http://www.umd.be/BRCA1/). In about 2-15% of patients tested for *BRCA* genes, the result is a "variant of unknown significance" (VUS) [16,17].

These unclassified variants are problematic for risk estimation and clinical management giving no clear indication as to whether or not the patient is at increased risk for developing cancer [18].

Deleterious mutations in one of the *BRCA* genes result in deficient homologous-recombination DNA repair and maintenance of telomere length; this can lead to subsequent accumulation of DNA damages (i.e. genetic aberrations) that predispose to carcinogenesis. The identification of a mutation in *BRCA* genes plays a relevant role in the management of hereditary cancer prevention, diagnosis and treatment.

In healthy *BRCA* carriers, the mutation detection may justify more intensive and personalized surveillance programs, chemopreventive approaches and prophylactic surgery that would not otherwise be justified by family history alone [19]. Particularly, being associated with a significant reduction in the risk of developing both breast and ovarian cancer, risk-reducing salpingo-oophorectomy is recommended to be performed by the age of 35-40 years after the completion of childbearing [19].

The identification of a mutation in already affected breast cancer patients may provide added information about the pathogenesis of these tumors, guiding treatment choices. These tumors have a major sensitivity to alkylating agents including platinum compounds [20] that are currently recommended for the treatment of locally advanced or metastatic *BRCA*-mutated breast cancer [7,21]. Another strategy for the treatment of *BRCA*-related breast cancer exploits the "synthetic lethality" concept [22]. On this basis, several trials are investigating the role of PARP inhibitors in the treatment of early and advanced *BRCA*-related breast cancer [23].

## 3. Impact of carrying a *BRCA* mutation on reproductive potential

Besides the consequences of *BRCA* function loss on breast cancer risk and management, these mutations can cause other potential non-oncological implications such as a negative impact on

female fertility (Figure 1). It has been hypothesized that carrying a *BRCA* mutations, especially *BRCA1*, can be associated with decreased ovarian reserve, increased fertility-related problems and primary ovarian insufficiency that can lead to infertility and early menopause [24].

There are biological plausible explanations for this hypothesis. In vitro experiments showed that *BRCA1* gene is highly expressed in human germ cells and blastocysts suggesting its possible role in gametogenesis and embryogenesis [25,26]. Animal experiments showed that mice harboring a *BRCA1* mutation have a lower ovarian reserve [27]. The *BRCA2* gene has also shown to have a key role in gametogenesis: adult females are characterized by a marked depletion of germ cells, and although some mutant oocytes can progress through the meiotic division phase, a high frequency of nuclear abnormalities is observed [28]. Furthermore, recent studies in mice and humans supported the crucial role of impaired DNA double-strand breaks (DSBs) repair in ovarian aging. The expression of *BRCA1* and other genes involved in DNA DSB repair has been shown to decline with age in the oocytes and granulosa cells [27,29–31]. The DSB repair pathway has a critical role in oocyte survival to resist and counteract genotoxic stress [27]. The impairment of DSB repair pathway seems to be associated with accelerated loss of ovarian follicular reserve as a consequence of the accumulation of DSBs in the oocytes [27]. Reproductive studies in transgenic mice have also shown that *BRCA1*- but not *BRCA2*-mutant mice produced a lower number of oocytes with smaller size in response to ovarian stimulation and fewer primordial follicles [32]. However, of note, the possible impact of *BRCA2* mutations on reproductive function may be present as well but less apparent due to the delayed decline of the normal *BRCA2* allele function at the end of the reproductive life [32].

Despite the strong rationale and preclinical data suggesting the possible negative impact of carrying a *BRCA* mutation on fertility potential, conflicting clinical data are available. Several studies have investigated the fertility outcomes (parity, age at menopause, infertility, and anti-mullerian hormone

[AMH] levels) of healthy women with *BRCA* mutation (Table 1) [33–46]. The majority of these studies did not show a significant difference among *BRCA* carriers and non-carriers, and when a negative association between *BRCA* mutation and fertility outcomes was found, this was mainly in *BRCA1* and not in *BRCA2* carriers. Nevertheless, most of the studies reporting age at menopause as outcome showed that *BRCA* carriers seem to develop menopause at an earlier age as compared to non-carriers. This is in line with the findings from preclinical studies supporting the crucial role of DNA DSB in ovarian aging, as well as recent comprehensive genetic analyses showing that several genes involved in DNA repair including *BRCA1* are associated with age at natural menopause [47,48].

More limited data exist in *BRCA*-mutated breast cancer patients (Table 2) [27,49–52]. Results were rather inconsistent with few studies suggesting a negative association between *BRCA* mutations, mostly *BRCA1*, and fertility outcomes. However, it should be noted that patient selection in these relatively small retrospective studies may have hampered a reliable comparison in reproductive outcomes between *BRCA*-mutation carriers and non-carriers (e.g. the use of prophylactic gynecologic surgery). Hence, a negative impact of carrying a *BRCA* mutation, mainly *BRCA1* but also *BRCA2* [28,53], on women's reproductive performance cannot be ruled out.

**4. Premature ovarian failure (POF) with anticancer treatments**

The development of treatment-induced POF is a possible consequence of anticancer treatments in young breast cancer patients [54]. The likelihood of developing treatment-induced POF may vary depending on the type and dose of chemotherapy agents used, the age of the patients at the time of treatment and the need for adjuvant endocrine therapy [55]. Using amenorrhea and resumption of menstrual function as indicators for the impact of chemotherapy on ovarian function, the most

commonly used regimens in breast cancer including cyclophosphamide, anthracyclines and taxanes are associated with an intermediate risk (40%-60%) of treatment-induced POF [56,57].

In *BRCA*-mutated breast cancer patients, specific issues should be considered on this regard. Due to both the possible existence of primary ovarian insufficiency [50] and the key role of DNA damage-induced follicle death [58], it can be hypothesized that the ovarian reserve of *BRCA*-mutated patients would be particularly sensitive to the gonadotoxic impact of anticancer treatments. However, the counseling of *BRCA*-mutated breast cancer patients to estimate the risk of treatment-induced POF is particularly difficult due to the very limited data available on this regard. Only one study has assessed so far the impact of chemotherapy on the risk of developing treatment-induced POF in the specific subgroup of *BRCA*-mutated breast cancer patients [51]. Valentini and colleagues performed a multicenter survey of 1,954 young premenopausal *BRCA*-mutated breast cancer patients of whom 1,426 received chemotherapy. Treatment-induced POF was defined as ≥ 2 years of amenorrhea commencing within 2 years from the initiation of chemotherapy and with no subsequent resumption of menstrual function. The probability of treatment-induced POF increased with age at diagnosis (7.2% for women ≤ 30 years vs. 33% for those between 31 and 44 years vs. 79% for patients ≥ 45 years; $p < 0.001$) and use of tamoxifen (52% vs. 19%; $p < 0.001$). Interestingly, the risk of developing this side effect was significantly higher for *BRCA2* carriers than for *BRCA1* carriers (46.8% vs. 32.7%; $p < 0.001$), also when restricting the analysis to the patients who did not receive tamoxifen (36.6% vs. 27.8%; $p = 0.04$). When comparing the age-specific probabilities of treatment-induced POF between the 1,426 carriers who received chemotherapy and 100 non-carriers, no significant difference was observed (35.6% in *BRCA* carriers vs. 49% in non-carriers; $p = 0.18$). There was no difference neither between non-carrier controls and *BRCA1* carriers ($p = 0.10$) or *BRCA2* carriers ($p = 0.50$) [51]. Some limitations should be considered in the interpretation of these results. Specifically, treatment-induced POF was defined based only on resumption of menstrual function as a surrogate indicator and was assessed retrospectively with a

questionnaire. More importantly, no detail on type and dose of chemotherapy received by the patients was available; finally, although the comparator group of non-carriers was selected using the same inclusion and exclusion criteria as the *BRCA* carriers, the number of patients included was limited and their baseline characteristics were not available.

Further research efforts should be put in place to better elucidate the impact of anticancer treatments on the ovarian function of *BRCA*-mutated patients. Moreover, to date, there are no specific data available on the possible added gonadotoxic impact of platinum agents. Although no specific toxicity has been shown in human primordial follicles with their use, platinum-based regimens are considered to have an intermediate risk of infertility [58]. Due to both their mechanism of action and the deficiency in the homologous-recombination-based DNA repair in *BRCA*-mutated patients, the ovarian toxicity with the use of these compounds might be associated with a particular negative impact. Considering the increasing trend of adding platinum agents to standard anthracycline- and taxane-based chemotherapy regimens for these patients [59], their impact on ovarian function and fertility potential needs to be urgently investigated. Furthermore, the activity of the PARP inhibitor olaparib in *BRCA*-mutated breast cancer patients has been recently demonstrated in the metastatic setting [60]; this opens the venue for future possibilities also in the early setting. These improvements in systemic anticancer therapy will add further complexity to the oncofertility counseling; the gonadotoxicity of PARP inhibitors is a research priority that is still unaddressed.

## 5. Available strategies for fertility preservation

Beyond the pros and cons of each strategy, specific issues should be taken into account during oncofertility counseling in *BRCA*-mutated breast cancer patients (Table 3).

### 5.1. Embryo/oocyte cryopreservation

Embryo/oocyte cryopreservation are standard strategies for fertility preservation in breast cancer patients [4–7]. These are the options with the most reliable results in the non-oncologic infertile population. However, limited data exist on their efficacy and safety in breast cancer patients [61,62], and even more limited information in those carrying a *BRCA* mutation.

In the largest series available, 33 (25.2%) of the 131 breast cancer patients who underwent controlled ovarian stimulation (COS) with the use of letrozole for embryo cryopreservation returned to the fertility clinic for embryo transfer after a median time of 5.25 years following oocyte retrieval [63]. The results did not differ from those expected in a comparable non-oncologic age group and time period, with an overall pregnancy rate of 65.0%, a live birth rate per embryo transfer of 45.0%, and an implantation rate of 40.7%. Seventeen out of 33 breast cancer survivors attempting pregnancy had at least one child; hence, the fertility preservation success rate was 51.5% per attempting woman [63]. Only 4 of the 33 patients (12%) included in this study had a *BRCA* mutation making it hard to draw any conclusions in this patient subset.

Two small studies with conflicting results investigated the response to COS of *BRCA*-mutated breast cancer patients [50,52,64]. Oktay and colleagues compared the response to COS (with a protocol that included the use of letrozole) between 12 *BRCA*-mutated breast cancer patients and 33 without mutations [50]. Low ovarian response rate (defined as retrieval of $\leq 4$ oocytes in women younger than 38 years) was significantly higher in *BRCA*-mutated as compared to *BRCA*-negative (33.3% vs. 3.3%; $p = 0.014$) patients. Interestingly, all *BRCA*-mutated patients with low response had *BRCA1* mutations. Mean oocyte numbers were significantly lower in *BRCA*-mutated than in *BRCA*-negative (7.9 vs. 11.3; $p = 0.025$) patients. As compared with controls, *BRCA1*-mutated but not *BRCA2*-mutated patients produced lower numbers of oocytes (7.4 vs. 12.4; $p = 0.025$) [50]. On the contrary, a more recent study evaluating the performance of COS (with a protocol that included tamoxifen in 19% of the cases) in 20 *BRCA*-mutated breast cancer patients did not find any

difference as compared to 36 *BRCA*-negative patients [52,64]. The study showed similar results between carriers and non-carriers in terms of oocytes collected (11.50 vs. 11.69; p = 0.92), number of zygotes (8.4 vs. 7.19; p = 0.57) and fertilization rates (70.6% vs. 59.66%; p = 0.11) [52,64]. Two main differences among these two studies should be considered in the interpretation of their results: 1) patient population (American women in one study [50] and Israeli patients in the other [52,64]); 2) use of different protocols for COS (antagonist protocol with the use of letrozole in one study [50], and different protocols [long agonist protocol in 53% and antagonist protocol in 47% of the cases, with 19% of patients exposed also to tamoxifen] in the second study [52,64]). Of note, only 32 *BRCA*-mutated breast cancer patients were included in these studies combined.

From a safety perspective, despite recent data were reassuring on the risk of developing breast cancer after fertility treatment with *in vitro* fertilization (IVF) procedures in the infertile non oncologic population [65], the short-term exposure to high estrogen levels during standard COS raises some safety concerns in breast cancer patients. Only one single-center prospective study investigating the safety of COS before the start of chemotherapy has been conducted so far in this setting [66]. All patients who underwent embryo cryopreservation received an antagonist protocol for COS including also the administration of letrozole to maintaining estrogen levels within physiological ranges during stimulation. Of 337 breast cancer patients included, 120 underwent COS while 217 did not undergo any fertility-preserving procedure and served as controls [66]. After a mean follow-up of 5 years, the study showed no difference in relapse-free survival between the two groups (hazard ratio [HR], 0.77; 95% confidence intervals [CI], 0.28-2.13; p = 0.61). In the entire study cohort, 188 patients underwent *BRCA* mutation test resulting in 47 *BRCA*-mutated cases, 127 *BRCA*-negative and 14 unverified results). Among the 47 *BRCA*-mutated patients, 26 underwent COS and 21 did not pursue any fertility-preserving procedure. Women in the COS group tended to have smaller tumor as compared to those in the control group (p = 0.02). Even in the *BRCA*-mutated population, no significant difference in relapse-free survival was observed among

the 2 groups, with one recurrence in the COS group and 2 in the control group (p = 0.57) [66].

The limited and conflicting data available highlights the need to pursue further research efforts in this field to achieve both long-term follow-up data and higher numbers to properly counsel *BRCA*-mutated breast cancer patients on the efficacy and safety of performing COS for embryo/oocyte cryopreservation before starting chemotherapy.

5.2. Cryopreservation of ovarian tissue

Ovarian tissue cryopreservation is an effective, yet still experimental, technique for fertility preservation in patients receiving cytotoxic therapies [4–6]. Although still experimental, ovarian tissue cryopreservation might be proposed to selected patients as prepubertal girls, but also in adults including some breast cancer patients who are scheduled for high gonadotoxic therapies and cannot delay anticancer treatments or with prior exposure to chemotherapy, or with contraindications to COS [56].

In *BRCA*-mutated breast cancer patients, limited data are available so far on the safety and efficacy of the procedure. Only one birth has been reported after transplantation of ovarian tissue in a *BRCA2*-mutated breast cancer patient [67]. Prior to chemotherapy, one ovary was cryopreserved and after the end of treatment the ovarian tissue was transplanted to the remaining ovary so that after her successful pregnancy the ovary could be removed [67].

Considering the general recommendation to pursue bilateral salpingo-oophorectomy before the age of 40 [19], ovarian tissue cryopreservation should be considered only in *BRCA*-mutated breast cancer patients diagnosed at a very young age (i.e. before the recommended age for prophylactic bilateral salpingo-oophorectomy) who cannot perform embryo/oocyte cryopreservation. However, for most of the patients who undergo ovarian tissue cryopreservation at the time of breast cancer

diagnosis, no information are available on their *BRCA* status. An ethical aspect to be considered is how to deal with frozen ovarian tissue collected from women with *BRCA* mutations. In the Norwegian experience, one breast cancer patient that had ovarian tissue harvesting before treatment and was then diagnosed with *BRCA1* and *BRCA2* mutations was advised against autotransplantation despite her interest in having a pregnancy [68]. As suggested by some authors, heterotopic subcutaneous transplantation of the tissue in the forearm or lower abdomen may be preferable to allow closer monitoring of the tissue [69]. Another potential approach in this setting is *in vitro* growth of isolated immature ovarian follicles without having to transplant the tissue back [70]. However, although the research on *in vitro* growth techniques is continuing to improve, the results with this approach have not been fruitful so far [70].

The lack of the data on the feasibility of this approach in *BRCA*-mutated breast cancer patients should be discussed during oncofertility counseling.

5.3. Temporary ovarian suppression with gonadotrophin-releasing hormone agonists (GnRHa) during chemotherapy

The role and clinical application of temporary ovarian suppression with GnRHa during chemotherapy has been actively debated over the past years [71–74]. However, recent findings have supported the efficacy of this strategy in breast cancer patients [75,76]. The three largest randomized studies on this topic (i.e. the PROMISE-GIM6, POEMS-SWOG S0230 and OPTION trials) showed similar results with a significant reduction in the risk of developing treatment-induced POF and higher pregnancy rates in patients receiving GnRHa during chemotherapy [77–79]. A meta-analysis including 12 randomized trials that investigated the role of this strategy in 1,231 breast cancer patients confirmed that temporary ovarian suppression with GnRHa during chemotherapy is associated with both a reduced risk of developing treatment-induced POF (odds

ratio [OR], 0.36; 95% CI, 0.23-0.57; $p < 0.001$) and an increased chance of future pregnancies (OR, 1.83; 95% CI, 1.02-3.28; $p = 0.041$) [80]. Taking into account these results, some current guidelines support the use of this strategy to preserve ovarian function and fertility in breast cancer patients [7,81].

In *BRCA*-mutated breast cancer patients, similar considerations as for cryopreservation of ovarian tissue can be made. Nevertheless, considering the efficacy of the strategy in breast cancer patients, the wide availability and the relatively low economical and personal cost of the procedure, it is reasonable to propose this strategy to *BRCA*-mutated breast cancer patients diagnosed at a very young age (i.e. before the recommended age for prophylactic bilateral salpingo-oophorectomy). The lack of data in this setting should be highlighted during oncofertility counseling and indeed more research efforts are needed to understand the magnitidue of benefit of this strategy in *BRCA* carriers.

**6. Safety of pregnancy in breast cancer survivors**

Despite approximately half of young women with newly diagnosed breast cancer desire to have a subsequent pregnancy after treatment [82], only 5%-15% of them achieve at least one full-term pregnancy after treatment [77,78]. The development of treatment-induced POF and also the potential concerns of both patients and providers related to the possible negative impact of pregnancy on the evolution of breast cancer can be possible explanations for these findings [83].

Although a growing amount of evidence over the last years has shown that pregnancy after breast cancer can be considered safe [84–86], very limited data are available on this regard in *BRCA*-mutated patients. In a recent survey conducted among physicians who attended the third “Breast Cancer in Young Women International Conference” (BCY3), more respondents were neutral in

answering the question regarding the safety of pregnancy after breast cancer in *BRCA*-mutated patients as compared to the whole young breast cancer population (34% vs. 17%) [87]. This probably reflects physicians' lack of confidence on the topic in this specific subgroup of patients for whom very limited evidence is currently available. In fact, to date, only one study investigated specifically the prognostic impact of pregnancy in *BRCA*-mutated patients [88]. This multicenter, retrospective cohort study included 128 pregnant cases and 269 matched non-pregnant controls diagnosed with breast cancer between 1985 and 2010. Among the pregnant cases, 75 women were diagnosed with breast cancer during pregnancy and 53 had a pregnancy following breast cancer. In the whole study population, no difference in breast cancer specific mortality was observed between pregnant cases and matched non-pregnant controls (adjusted HR, 0.76; 95% CI, 0.31-1.91; p = 0.56). Similar results were also observed in the subgroup analysis when considering only the small subgroup of patients with pregnancy following breast cancer (adjusted HR, 0.73; 95% CI, 0.21-2.68; p = 0.64) [88]. However, due to the limited number of patients included in the analysis, no solid conclusion can be drawn from this study to counsel *BRCA* mutated survivors on the safety of having a pregnancy after breast cancer diagnosis. Nevertheless, although more research efforts in this field are needed, it is biologically unlikely to expect a different prognostic effect of pregnancy between patients with and without *BRCA*-mutations.

An international prospective study conducted by the IBCSG with the collaboration of BIG and NABCG is currently ongoing to investigate the feasibility and safety of a temporary interruption of endocrine therapy to allow pregnancy in breast cancer patients (the POSITIVE study) [89]. The study can give important information also for patients with *BRCA* mutations, particularly for those with *BRCA2* mutations who often develop hormone receptor-positive tumors and are candidates for adjuvant endocrine therapy.

**7. Pre-implantation genetic test**

Besides the indication of undergoing preventive bilateral salpingo-oophorectomy, many *BRCA*-mutated women are confronted with a true reproductive decision-making dilemma as a consequence of the 50% risk of transmitting the mutated gene to their children. They either consider conceiving naturally with or without prenatal diagnosis (PND) or go through IVF/intracytoplasmic sperm injection (ICSI) for preimplantation genetic diagnosis (PGD) [90].

In PND, a chorionic villi sampling is performed during the first trimester of pregnancy with the possibility of pregnancy termination if the fetus carries the mutation. However, to terminate the pregnancy for hereditary breast and ovarian cancer risk seems unacceptable to most couples [91]. In the study by Derks-Smeets and colleagues on reproductive decision-making in couples with *BRCA* mutations, 4 out of 18 opted for PND and one couple decided to terminate the pregnancy for an affected fetus [91]. In a qualitative interview study, only one woman out of 25 participants decided to do PND [92]. She had had breast cancer in her 20's and she did not want to risk transmitting the mutation (PGD was not available when she wished to have a child). However, once she got pregnant and underwent fetal ultrasound, it became inconceivable for her to go through pregnancy termination regardless of genetic testing results [92]. Personal consideration and willingness to go through PND appear to be higher in women who are older, have higher education level, prior history of breast or ovarian cancer and in those who desire to conceive more quickly and naturally [93].

In case of PGD, the mutation is characterized by a previous DNA analysis of the carrier, her partner, and a first-degree relative who is also a carrier. Associated informative polymorphic markers either intragenic or closely linked to the mutated gene are categorized, and subsequently used in polymerase chain reaction (PCR) to perform the genetic diagnosis [94,95]. For this purpose, patients undergo COS for IVF/ICSI and on the third day of embryo development, a biopsy of one or

two blastomeres is performed in order to proceed with the PCR analysis. If the embryo is unaffected and has continued its development, an embryo transfer is done on day 5 at blastocyst stage. In 2003, the European Society of Human Reproduction and Embryology has accepted PGD for late onset diseases such as hereditary breast and ovarian cancer [96]. During the last decade, several authors have reported on the awareness and acceptability of PGD in couples of reproductive age with *BRCA* mutations [90,91,93,95,97]. Assessment was done through individual or group interviews as well as by means of questionnaires. In the survey by Menon and colleagues, 75% of respondents (of whom 50% had a history of breast cancer) considered PGD acceptable in general, and 37.5% of those who completed their family project would have considered doing it if it had been offered at the time [97]. A better knowledge of PGD showed to be correlated with younger age, higher education level, not having children, wishing to conceive rapidly; higher acceptability of the procedure (79.5%) was positively correlated with personal history of breast/ovarian cancer [93]. However, only 39.2% of respondents would personally consider PGD for hereditary breast and ovarian cancer as compared to 58% for other severe genetic diseases [93]. Couples who considered PGD acceptable but who wouldn't personally do it pointed out mostly physical and psychological burden of the entire process especially in fertile patients, relatively low pregnancy rate, delaying childbearing and the discarding of affected embryos that might not develop the illness [90–92,98]. A recent observational cohort study evaluated the efficiency of the procedure in 70 couples undergoing IVF for PGD: 59% of women were carriers and 14% had a history of breast cancer [91]. A total of 145 PGD cycles were performed in 720 embryos: 40.8% were not affected, 43.2% were affected, 9.7% were abnormal and 6.3% had no diagnosis. In 61% of fresh cycles, one or two embryos were transferred resulting in a pregnancy rate of 23.9% per cycle started. In frozen embryo transfer cycles, pregnancy rate was 26.5% per cycle. Overall, 28 out of 31 singletons and 8 out of 10 twins (5 pregnancies) were born alive following the procedure, including 2 out of 3 women who had PGD on embryos collected for fertility preservation before breast cancer therapy [91].

## 8. Conclusions and future perspective

Fertility and pregnancy-related issues represent one of the main areas of concerns for young women with breast cancer. Carrying a *BRCA* mutation adds additional burden on this regard due to the specific issues that should be considered when counseling these patients. Although for the majority of young women with breast cancer, the information on the *BRCA* mutational status is not known during the oncofertility counseling at the time of diagnosis, most of them are nowadays candidates to undergo genetic testing [99]. This is expected to become even more common and challenging with the introduction of multi-gene panel sequencing technologies that are revolutionizing germline risk assessment for hereditary breast cancer [100,101].

Despite the availability of a growing amount of data to counsel young women with breast cancer on the safety and efficacy of the different strategies for fertility preservation as well as the feasibility of having a pregnancy after diagnosis, numerous challenges remain for patients carrying *BRCA* mutations due to both their specific needs and the lack of data on these topics. Whenever available and allowed by national laws and regulations, egg donation and surrogacy represent other potential options for breast cancer patients including those with *BRCA* mutations [102]. Nevertheless, in some cases, despite all the possible efforts, adoption remains the only option to enable survivors to become a parent. However, it should be noted that cancer survivors may encounter barriers as potential adoptive parents due to their medical history [103], and these difficulties might be even more important for *BRCA*-mutated patients.

Reproduction studies to address the specific issues of *BRCA*-mutated breast cancer patients, including the impact of the mutation on their fertility potential, the safety and efficacy of the different strategies for fertility preservation, and the feasibility of having a pregnancy after

diagnosis, should be considered a research priority with the final goal to improve the oncofertility counseling of these patients.

**Acknowledgements**

Dr. Matteo Lambertini acknowledges the support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet in Brussels (Belgium).

**Funding**

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Disclosure**

Hatem A. Azim Jr. MD, PhD reports employment at Innate Pharma at the time this manuscript was concluded; this employment is not related in any sort to the subject of the current manuscript. All the other authors declare no conflict of interest.

**References**

1. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 2016;66(1):31–42.

2. Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, et al. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med. 2015;372(5):436–46.

3. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104(5):386–405.

4. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2013;31(19):2500–10.

5. Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-170.

6. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214–23.

7. Paluch-Shimon S, Pagani O, Partridge AH, Bar-Meir E, Fallowfield L, Fenlon D, et al. Second international consensus guidelines for breast cancer in young women (BCY2). Breast. 2016;26:87–99.

8. Wooster R, Weber BL. Breast and ovarian cancer. N Engl J Med. 2003;348(23):2339–47.

9. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer. 2012;12(1):68–78.

10. Hartmann LC, Lindor NM. The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer. N Engl J Med. 2016;374(5):454–68.

11. Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 2017;29(4):243-52.

12. Kelvin JF, Thom B, Benedict C, Carter J, Corcoran S, Dickler MN, et al. Cancer and Fertility Program Improves Patient Satisfaction With Information Received. J Clin Oncol. 2016;34(15):1780–6.

13. Lambertini M, Anserini P, Fontana V, Poggio F, Iacono G, Abate A, et al. The PREgnancy and FERtility (PREFER) study: an Italian multicenter prospective cohort study on fertility preservation and pregnancy issues in young breast cancer patients. BMC Cancer. 2017;17(1):346.

14. Lambertini M, Del Mastro L. Fertility preservation in BRCA-mutated breast cancer patients. Breast Cancer Manag. 2016; 5(2):61–8.

15. Lambertini M, Ginsburg ES, Partridge AH. Update on fertility preservation in young women undergoing breast cancer and ovarian cancer therapy. Curr Opin Obstet Gynecol. 2015;27(1):98–107.

16. Eggington JM, Bowles KR, Moyes K, Manley S, Esterling L, Sizemore S, et al. A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes. Clin Genet. 2014;86(3):229–37.

17. Lindor NM, Goldgar DE, Tavtigian SV, Plon SE, Couch FJ. BRCA1/2 sequence variants of uncertain significance: a primer for providers to assist in discussions and in medical management. The Oncologist. 2013;18(5):518–24.

18. Borg A, Haile RW, Malone KE, Capanu M, Diep A, Törngren T, et al. Characterization of BRCA1 and BRCA2 deleterious mutations and variants of unknown clinical significance in unilateral and bilateral breast cancer: the WECARE study. Hum Mutat. 2010;31(3):E1200-1240.

19. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016;27(suppl 5):v103–10.

20. Gerratana L, Fanotto V, Pelizzari G, Agostinetto E, Puglisi F. Do platinum salts fit all triple negative breast cancers? Cancer Treat Rev. 2016;48:34–41.

21. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol.

2015;26(8):1533–46.

22. Toss A, Cortesi L. Molecular Mechanisms of PARP Inhibitors in BRCA-related Ovarian Cancer. J Cancer Sci Ther 2013;5:409-416.

23. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med. 2015;13:188.

24. de la Noval BD. Potential implications on female fertility and reproductive lifespan in BRCA germline mutation women. Arch Gynecol Obstet. 2016;294(5):1099–103.

25. Giscard d'Estaing S, Perrin D, Lenoir GM, Guérin JF, Dante R. Upregulation of the BRCA1 gene in human germ cells and in preimplantation embryos. Fertil Steril. 2005;84(3):785–8.

26. Eakin CM, Maccoss MJ, Finney GL, Klevit RE. Estrogen receptor alpha is a putative substrate for the BRCA1 ubiquitin ligase. Proc Natl Acad Sci U S A. 2007;104(14):5794–9.

27. Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. Sci Transl Med. 2013;5(172):172ra21.

28. Sharan SK, Pyle A, Coppola V, Babus J, Swaminathan S, Benedict J, et al. BRCA2 deficiency in mice leads to meiotic impairment and infertility. Dev Camb Engl. 2004;131(1):131–42.

29. Govindaraj V, Keralapura Basavaraju R, Rao AJ. Changes in the expression of DNA double strand break repair genes in primordial follicles from immature and aged rats. Reprod Biomed Online. 2015;30(3):303–10.

30. Zhang D, Zhang X, Zeng M, Yuan J, Liu M, Yin Y, et al. Increased DNA damage and repair deficiency in granulosa cells are associated with ovarian aging in rhesus monkey. J Assist Reprod Genet. 2015;32(7):1069–78.

31. Govindaraj V, Krishnagiri H, Chauhan MS, Rao AJ. BRCA-1 Gene Expression and Comparative Proteomic Profile of Primordial Follicles from Young and Adult Buffalo (Bubalus bubalis) Ovaries. Anim Biotechnol. 2016;1–10.

32. Oktay K, Turan V, Titus S, Stobezki R, Liu L. BRCA Mutations, DNA Repair Deficiency, and Ovarian Aging. Biol Reprod. 2015;93(3):67.

33. Gal I, Sadetzki S, Gershoni-Baruch R, Oberman B, Carp H, Papa MZ, et al. Offspring gender ratio and the rate of recurrent spontaneous miscarriages in jewish women at high risk for breast/ovarian cancer. Am J Hum Genet. 2004;74(6):1270–5.

34. Friedman E, Kotsopoulos J, Lubinski J, Lynch HT, Ghadirian P, Neuhausen SL, et al. Spontaneous and therapeutic abortions and the risk of breast cancer among BRCA mutation carriers. Breast Cancer Res. 2006;8(2):R15.

35. Moslehi R, Singh R, Lessner L, Friedman JM. Impact of BRCA mutations on female fertility and offspring sex ratio. Am J Hum Biol. 2010;22(2):201–5.

36. Pal T, Keefe D, Sun P, Narod SA, Hereditary Breast Cancer Clinical Study Group. Fertility in women with BRCA mutations: a case-control study. Fertil Steril. 2010;93(6):1805–8.

37. Smith KR, Hanson HA, Mineau GP, Buys SS. Effects of BRCA1 and BRCA2 mutations on female fertility. Proc Biol Sci. 2012;279(1732):1389–95.

38. Finch A, Valentini A, Greenblatt E, Lynch HT, Ghadirian P, Armel S, et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril. 2013;99(6):1724–8.

39. Collins IM, Milne RL, McLachlan SA, Friedlander M, Hickey M, Weideman PC, et al. Do BRCA1 and BRCA2 mutation carriers have earlier natural menopause than their noncarrier relatives? Results from the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. J Clin Oncol. 2013;31(31):3920–5.

40. Lin WT, Beattie M, Chen L-M, Oktay K, Crawford SL, Gold EB, et al. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer. 2013;119(9):1652–9.

41. Michaelson-Cohen R, Mor P, Srebnik N, Beller U, Levy-Lahad E, Eldar-Geva T. BRCA mutation carriers do not have compromised ovarian reserve. Int J Gynecol Cancer. 2014;24(2):233–

7.

42. Wang ET, Pisarska MD, Bresee C, Chen Y-DI, Lester J, Afshar Y, et al. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil Steril. 2014;102(6):1723–8.

43. Kwiatkowski F, Arbre M, Bidet Y, Laquet C, Uhrhammer N, Bignon Y-J. BRCA Mutations Increase Fertility in Families at Hereditary Breast/Ovarian Cancer Risk. PloS One. 2015;10(6):e0127363.

44. van Tilborg TC, Broekmans FJ, Pijpe A, Schrijver LH, Mooij TM, Oosterwijk JC, et al. Do BRCA1/2 mutation carriers have an earlier onset of natural menopause? Menopause N Y N. 2016;23(8):903–10.

45. Phillips K-A, Collins IM, Milne RL, McLachlan SA, Friedlander M, Hickey M, et al. Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations. Hum Reprod. 2016;31(5):1126–32.

46. van Tilborg TC, Derks-Smeets IAP, Bos AME, Oosterwijk JC, van Golde RJ, de Die-Smulders CE, et al. Serum AMH levels in healthy women from BRCA1/2 mutated families: are they reduced? Hum Reprod. 2016;31(11):2651–9.

47. Stolk L, Perry JRB, Chasman DI, He C, Mangino M, Sulem P, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. Nat Genet. 2012;44(3):260–8.

48. Day FR, Ruth KS, Thompson DJ, Lunetta KL, Pervjakova N, Chasman DI, et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. Nat Genet. 2015;47(11):1294–303.

49. Rzepka-Górska I, Tarnowski B, Chudecka-Głaz A, Górski B, Zielińska D, Tołoczko-Grabarek A. Premature menopause in patients with BRCA1 gene mutation. Breast Cancer Res Treat. 2006;100(1):59–63.

50. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and

breast/ovarian cancer risks. J Clin Oncol. 2010;28(2):240–4.

51. Valentini A, Finch A, Lubinski J, Byrski T, Ghadirian P, Kim-Sing C, et al. Chemotherapy-induced amenorrhea in patients with breast cancer with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2013;31(31):3914–9.

52. Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, et al. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 2015;104(5):1162–7.

53. Connor F, Bertwistle D, Mee PJ, Ross GM, Swift S, Grigorieva E, et al. Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation. Nat Genet. 1997;17(4):423–30.

54. Poggio F, Levaggi A, Lambertini M. Chemotherapy-induced premature ovarian failure and its prevention in premenopausal breast cancer patients. Expert Rev Quality Life Cancer Care. 2016;1(1):5-7.

55. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–31.

56. Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016;14(1):1.

57. Lambertini M, Ceppi M, Cognetti F, Cavazzini G, De Laurentiis M, De Placido S, et al. Dose-dense adjuvant chemotherapy in premenopausal breast cancer patients: A pooled analysis of the MIG1 and GIM2 phase III studies. Eur J Cancer. 2017;71:34–42.

58. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol. 2016;12(20):2333–44.

59. Lambertini M, Poggio F, Vaglica M, Blondeaux E, Del Mastro L. News on the medical treatment of young women with early-stage HER2-negative breast cancer. Expert Opin Pharmacother. 2016;17(12):1643–55.

60. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017; [Epub ahead of print].

61. Lambertini M, Pescio MC, Viglietti G, Goldrat O, Del Mastro L, Anserini P, Demeestere I. Methods of controlled ovarian stimulation for embryo/oocyte cryopreservation in breast cancer patients. Expert Rev Quality Life Cancer Care 2017; 2(1):47-59.

62. Massarotti C, Scaruffi P, Lambertini M, Remorgida V, Del Mastro L, Anserini P. State of the art on oocyte cryopreservation in female cancer patients: A critical review of the literature. Cancer Treat Rev. 2017;57:50–7.

63. Oktay K, Turan V, Bedoschi G, Pacheco FS, Moy F. Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol. 2015;33(22):2424–9.

64. Shapira M, Raanani H, Meirow D. IVF for fertility preservation in breast cancer patients--efficacy and safety issues. J Assist Reprod Genet. 2015;32(8):1171–8.

65. van den Belt-Dusebout AW, Spaan M, Lambalk CB, Kortman M, Laven JSE, van Santbrink EJP, et al. Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. JAMA. 2016;316(3):300–12.

66. Kim J, Turan V, Oktay K. Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer. J Clin Endocrinol Metab. 2016;101(4):1364–71.

67. Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. J Assist Reprod Genet. 2017;34(3):325–36.

68. Tanbo T, Greggains G, Storeng R, Busund B, Langebrekke A, Fedorcsak P. Autotransplantation of cryopreserved ovarian tissue after treatment for malignant disease - the first

Norwegian results. Acta Obstet Gynecol. 2015;94(9):937–41.

69. Rodriguez-Wallberg KA, Oktay K. Fertility preservation and pregnancy in women with and without BRCA mutation-positive breast cancer. The Oncologist. 2012;17(11):1409–17.

70. Telfer EE, McLaughlin M. In vitro development of ovarian follicles. Semin Reprod Med. 2011;29(1):15–23.

71. Turner NH, Partridge A, Sanna G, Di Leo A, Biganzoli L. Utility of gonadotropin-releasing hormone agonists for fertility preservation in young breast cancer patients: the benefit remains uncertain. Ann Oncol. 2013;24(9):2224–35.

72. Blumenfeld Z, Katz G, Evron A. "An ounce of prevention is worth a pound of cure": the case for and against GnRH-agonist for fertility preservation. Ann Oncol. 2014;25(9):1719–28.

73. Rodriguez-Wallberg K, Turan V, Munster P, Oktay K. Can ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) preserve fertility in cancer patients? Ann Oncol. 2016;27(2):257.

74. Lambertini M, Falcone T, Unger JM, Phillips K-A, Del Mastro L, Moore HCF. Debated Role of Ovarian Protection With Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Women With Cancer. J Clin Oncol. 2017;35(7):804–5.

75. Lambertini M, Dellepiane C, Viglietti G, Del Mastro L. Pharmacotherapy to protect ovarian function and fertility during cancer treatment. Expert Opin Pharmacother. 2017;18(8):739–42.

76. Lambertini M, Del Mastro L, Viglietti G, Pondé NF, Solinas C, de Azambuja E. Ovarian Function Suppression in Premenopausal Women with Early-Stage Breast Cancer. Curr Treat Options Oncol. 2017;18(1):4.

77. Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, et al. Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival: A Randomized Clinical Trial. JAMA. 2015;314(24):2632–40.

78. Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.

79. Leonard R, Adamson D, Bertelli G, Mansi J, Yellowlees A, Dunlop J, et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol. 2017; [Epub ahead of print].

80. Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015;26(12):2408–19.

81. Lambertini M, Cinquini M, Moschetti I, Peccatori FA, Anserini P, Valenzano Menada M, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. Eur J Cancer. 2017;71:25–33.

82. Letourneau JM, Smith JF, Ebbel EE, Craig A, Katz PP, Cedars MI, et al. Racial, socioeconomic, and demographic disparities in access to fertility preservation in young women diagnosed with cancer. Cancer. 2012;118(18):4579–88.

83. Biglia N, Torrisi R, D'Alonzo M, Codacci Pisanelli G, Rota S, Peccatori FA. Attitudes on fertility issues in breast cancer patients: an Italian survey. Gynecol Endocrinol. 2015;31(6):458–64.

84. Azim HA Jr, Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31(1):73–9.

85. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Safety of pregnancy in patients (pts) with history of estrogen receptor positive (ER+) breast cancer (BC): long-term follow-up analysis from a multicenter study. J Clin Oncol 2017; abstract.

86. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before,

during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016;160(2):347–60.

87. Lambertini M, Di Maio M, Pagani O, Demeestere I, Del Mastro L, Loibl S, Partridge AH, Azim HA Jr., Peccatori FA. A survey on physicians' knowledge, practice and attitudes on fertility and pregnancy issues in young breast cancer patients. BCC 2017 - St. Gallen Consensus Conference; abstract P189.

88. Valentini A, Lubinski J, Byrski T, Ghadirian P, Moller P, Lynch HT, et al. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2013;142(1):177–85.

89. Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: Are young patients willing to participate in clinical studies? Breast. 2015;24(3):201–7.

90. Quinn GP, Vadaparampil ST, Tollin S, Miree CA, Murphy D, Bower B, et al. BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. Fertil Steril. 2010;94(6):2473–5.

91. Derks-Smeets I a. P, Gietel-Habets JJG, Tibben A, Tjan-Heijnen VCG, Meijer-Hoogeveen M, Geraedts JPM, et al. Decision-making on preimplantation genetic diagnosis and prenatal diagnosis: a challenge for couples with hereditary breast and ovarian cancer. Hum Reprod. 2014;29(5):1103–12.

92. Ormondroyd E, Donnelly L, Moynihan C, Savona C, Bancroft E, Evans DG, et al. Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis. Eur J Hum Genet. 2012;20(1):4–10.

93. Gietel-Habets JJG, de Die-Smulders CEM, Derks-Smeets I a. P, Tibben A, Tjan-Heijnen VCG, van Golde R, et al. Awareness and attitude regarding reproductive options of persons carrying a BRCA mutation and their partners. Hum Reprod. 2017;32(3):588–97.

94. Sagi M, Weinberg N, Eilat A, Aizenman E, Werner M, Girsh E, et al. Preimplantation genetic diagnosis for BRCA1/2--a novel clinical experience. Prenat Diagn. 2009;29(5):508–13.

95. Derks-Smeets IAP, de Die-Smulders CEM, Mackens S, van Golde R, Paulussen AD, Dreesen J, et al. Hereditary breast and ovarian cancer and reproduction: an observational study on the suitability of preimplantation genetic diagnosis for both asymptomatic carriers and breast cancer survivors. Breast Cancer Res Treat. 2014;145(3):673–81.

96. Shenfield F, Pennings G, Devroey P, Sureau C, Tarlatzis B, Cohen J, et al. Taskforce 5: preimplantation genetic diagnosis. Hum Reprod. 2003;18(3):649–51.

97. Menon U, Harper J, Sharma A, Fraser L, Burnell M, ElMasry K, et al. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod. 2007;22(6):1573–7.

98. Rubin LR, Werner-Lin A, Sagi M, Cholst I, Stern R, Lilienthal D, et al. "The BRCA clock is ticking!": negotiating medical concerns and reproductive goals in preimplantation genetic diagnosis. Hum Fertil. 2014;17(3):159–64.

99. Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 Mutation Testing in Young Women With Breast Cancer. JAMA Oncol. 2016;2(6):730–6.

100. Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. J Clin Oncol. 2016;34(13):1460–8.

101. Thompson ER, Rowley SM, Li N, McInerny S, Devereux L, Wong-Brown MW, et al. Panel Testing for Familial Breast Cancer: Calibrating the Tension Between Research and Clinical Care. J Clin Oncol. 2016;34(13):1455–9.

102. Luke B, Brown MB, Missmer SA, Spector LG, Leach RE, Williams M, et al. Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016;31(1):183–9.

103. Rosen A. Third-party reproduction and adoption in cancer patients. J Natl Cancer Inst Monogr. 2005;(34):91–3.

**FIGURE LEGEND**

**Figure 1.** *BRCA* mutations and their potential negative impact on reproductive potential.

**FERTILITY AND PREGNANCY ISSUES IN *BRCA*-MUTATED BREAST CANCER PATIENTS**

**HIGHLIGHTS**

- Fertility and pregnancy-related issues are one of the main areas of concerns for young women with breast cancer.
- Carrying a germline deleterious *BRCA* mutation adds additional burden on this regard.
- Specific needs and issues should be considered when counseling *BRCA*-mutated breast cancer patients.
- Reproduction studies in *BRCA*-mutated breast cancer patients should be considered a research priority.

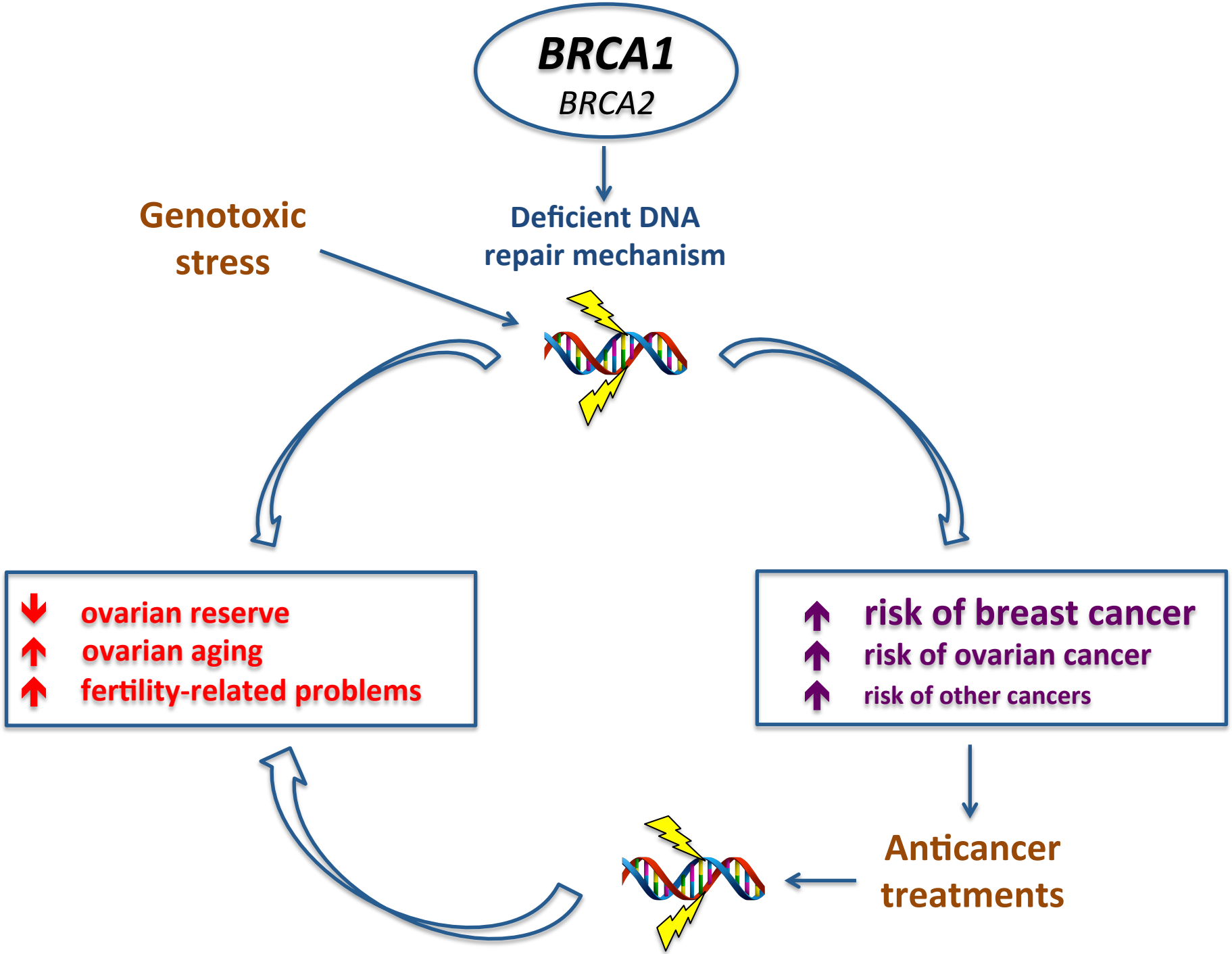
BRCA1
BRCA2
Genotoxic stress
Deficient DNA repair mechanism
ovarian reserve
ovarian aging
fertility-related problems
risk of breast cancer
risk of ovarian cancer
risk of other cancers
Anticancer treatments

**Table 1.** Impact of carrying a *BRCA* mutation on reproductive potential in healthy carriers.

| Author | Type of study | Number of *BRCA* carriers | Number of non-carriers | Fertility endpoints | Results (carriers vs. non-carriers) | Overall result |
|---|---|---|---|---|---|---|
| Gal et al. 2004 [33] | Case-control study | 393* | 424* | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>9 vs. 5; p=0.18<br>2.33 vs. 2.5; p=0.045 | No difference |
| Friedman et al. 2006 [34] | Case-control study | 2,828 | 657 | Parity:<br>-No. children (mean) | <br>2.38 vs. 2.43 | No difference |
| Moslehi et al. 2010 [35] | Case-control study | 96 | 164 | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>8.6 vs. 11.1<br>2.56 vs. 2.59 | No difference |
| | | | | Infertility:<br>-Fertility medication, % | <br>10.4 vs. 9.8 | |
| Pal et al. 2010 [36] | Case-control study | 2,254* | 764* | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>23.1 vs. 24.4; p=0.54<br>1.9 vs. 1.9; p=0.95 | No difference |
| | | | | Age at first birth (mean) years | 25.6 vs. 25.5; p=0.82 | |
| | | | | Infertility:<br>-Fertility problems, %<br>-Fertility medication, %<br>-Fertility treatment, % | <br>14.4 vs. 14.1; p=0.81<br>3.8 vs. 4.9; p=0.28<br>0.5 vs. 0.3; p=0.39 | |
| Smith et al. 2012 [37] | Retrospective analysis within 2 longitudinal studies | 181 | 2,715 | Parity:<br>-No. children (mean) | <br>6.22 vs. 4.19; p<0.001<br>4.13 vs. 3.40; p=0.01 | Difference favoring *BRCA* carriers |
| | | | | Age at first birth (mean) years | 23.44 vs. 24.18; p=0.23<br>23.09 vs. 24.42; p=0.004 | |
| Finch et al. 2013 [38] | Observational study (survey) | 908 | 908 | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>31.6 vs. 33.7; p=0.35<br>1.67 vs. 1.53; p=0.15 | No difference in fertility outcomes; earlier age at |
| | | | | Age at first birth (mean) years | 26.60 vs. 26.93; p=0.27 | |
| | | | | Age at menopause (mean) years | 49.0 vs. 50.3; p=0.001 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Infertility:<br>-Fertility problems, %<br>-Fertility medication, %<br>-Fertility treatment, % | <br>12.5 vs.13.7; p=0.46<br>6.0 vs. 7.0; p=0.41<br>0.8 vs. 2.1; p=0.04 | menopause for *BRCA* carriers |
| Collins et al. 2013 [39] | Retrospective analysis within a prospective cohort study | 819 | 1,021 | Parity:<br>-Nulliparous, % | <br>26.5 vs. 25.1; p=0.80/p=0.28 | No difference |
| | | | | Age at first birth (mean) years | 25 vs. 25; p=0.81/p=0.83 | |
| | | | | Age at menopause (mean) years | 51 vs. 51-52; p=0.7/p=0.9 | |
| | | | | Infertility:<br>-Fertility treatment, % | <br>4.9 vs. 6.0; p=0.82/p=0.20 | |
| Lin et al. 2013 [40] | Cross-sectional study | 382 | 765 | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>39.4 vs. 25.5; p<0.001<br>1.3 vs. 1.5; p=0.0017 | Difference favoring non-carriers |
| | | | | Age at menopause (mean) years | 50 vs. 53; p<0.001 | |
| Michaelson-Cohen et al. 2014 [41] | Cross-sectional study | 41 | 324 | AMH level (mean) ng/ml | 2.71 vs. 2.02; p=0.27 | No difference |
| Wang et al. 2014 [42] | Cross-sectional study | 89 | 54 | Parity:<br>-Nulliparous, % | <br>22/37 vs. 25; p=0.512 | Difference in AMH levels favoring non-carriers over *BRCA1* carriers (no difference in *BRCA2*) |
| | | | | AMH level (mean) ng/ml<br>*BRCA1* vs controls<br>*BRCA2* vs controls | <br>0.53 vs. 1.05; p=0.026<br>0.73 vs. 1.05; p=0.470 | |
| Kwiatkowski et al. 2015 [43] | Retrospective analysis | 583* | 364* | Parity:<br>-Nulliparous, %<br>-No. children (mean) | <br>9.1 vs. 16.0; p=0.003<br>1.8 vs. 1.5; p=0.002 | Difference favoring *BRCA* carriers |
| | | | | Age at first birth (mean) years | 24.9 vs. 24.7 p=0.97 | |
| Van Tilborg et al. 2016 [44] | Cross-sectional study | 1,208* | 2,211* | Parity:<br>-Nulliparous, % | <br>23.9 vs. 20.7; p=0.04 | Difference favoring non-carriers |
| | | | | Age at menopause (mean) years | 53 vs. 53; p=0.207<br>51 vs. 53; p=0.012 | |
| Phillips et al. | Cross-sectional | 319 | 374 | Parity: | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2016 [45] | study | | | -Nulliparous, % | 27/36 vs. 30/30; p=0.50/p=0.33 | Difference in AMH levels favoring non-carriers over *BRCA1* carriers (no difference in *BRCA2*) |
| | | | | Age at first birth (mean) years | 24.9/25.7 vs. 25.0/25.6; p=0.76/p=0.87 | |
| | | | | Infertility:<br>-Fertility treatment, % | <br>6/5 vs. 5/7; p=0.65/p=0.64 | |
| | | | | AMH level<br>*BRCA1* vs controls<br>*BRCA2* vs controls | <br>25% lower; p=0.02<br>No difference; p=0.94 | |
| Van Tilborg et al. 2016 [46] | Cross-sectional study | 124 | 131 | Parity:<br>-Nulliparous, % | <br>58 vs. 41; p=0.008 | Difference favoring non-carriers; no difference in AMH levels |
| | | | | Age at first birth (mean) years | 29 vs. 28; p=0.21 | |
| | | | | Infertility:<br>-Fertility problems, %<br>-Fertility treatment, % | <br>30 vs. 15; p=0.03<br>44 vs. 36; p=0.70 | |
| | | | | AMH level (median) µg/l | 1.90 vs. 1.80; p=0.34 | |

* Included also women with prior history of breast cancer

Abbreviations: AMH, anti-mullerian hormone.

**Table 2.** Impact of carrying a *BRCA* mutation on reproductive potential in breast cancer patients.

| **Author** | **Type of study** | **Number of *BRCA* carriers** | **Number of non-carriers** | **Fertility endpoints** | **Results (carriers vs. non-carriers)** | **Overall result** |
|---|---|---|---|---|---|---|
| Rzepka-Gorska et al. 2006 [49] | Case-control study | 39 | 80 | Age at menopause (mean) years | 45.3 vs. 48.2; p=0.0277 | Difference favoring non-carriers over *BRCA1* carriers (no *BRCA2* included) |
| Oktay et al. 2010 [50] | Prospective cohort study | 12 | 33 | ART performance:<br>-Oocyte yeld (mean) No.<br>-Poor response rate**, % | <br>7.9 vs. 11.3; p=0.025<br>33.3 vs. 3.3; p=0.014 | Difference favoring non-carriers over *BRCA1* carriers (no difference in *BRCA2*) |
| Valentini et al. 2013 [51] | Observational study (survey) | 1,426 | 100 | Chemotherapy-induced amenorrhea, % | 25.6 vs. 49; p=0.18 | No difference |
| Titus et al. 2013 [27] | Cross-sectional study | 24 | 60 | AMH level (mean) ng/ml<br>*BRCA1* vs controls<br>*BRCA2* vs controls | <br>1.22 vs. 2.23; p<0.001<br>1.12 vs. 2.23; p<0.001<br>1.39 vs. 2.23; p<0.127 | AMH levels favoring non-carriers over *BRCA1* carriers (no difference in *BRCA2*) |
| Shapira et al. 2015 [52] | Retrospective cohort study | 62* | 62* | ART performance:<br>-Oocyte yeld (mean) No.<br>-Poor response rate*, % | <br>13.75 vs. 14.75; p=0.49<br>8.06 vs. 6.45; p=1.00 | No difference |

* Included also women without prior history of breast cancer

** Defined as retrieval of ≤ 4 oocytes in women younger than 38 years

Abbreviations: AMH, anti-mullerian hormone.

**Table 3.** Available strategies for fertility preservation in young women with breast cancer and recommendations in *BRCA*-mutated patients.

| Strategy | Indication in breast cancer patients | Issues to be considered in *BRCA* mutated breast cancer patients | Indication in *BRCA* mutated breast cancer patients |
|---|---|---|---|
| **Embryo/oocyte cryopreservation** | Yes (standard) | - Possible lower response to controlled ovarian stimulation<br>- No data on pregnancy and fertility preservation outcomes | Yes (standard) |
| **Cryopreservation of ovarian tissue** | Yes (experimental) | - High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years<br>- No data on the efficacy and safety of the procedure (only one pregancy reported in a *BRCA2*-mutated breast cancer patient) | To be considered only in patients diagnosed at a very young age who cannot perform embryo/oocyte cryopreservation |
| **Temporary ovarian suppression with GnRHa during chemotherapy** | Yes (standard) | - High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years<br>- No data on the efficacy and safety of the procedure | To be considered only in patients diagnosed at a very young age |

Abbreviation: GnRHa, gonadotrophin-releasing hormone agonists.