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Complications of Treatment

Fertility And Pregnancy Issues In *Brc*a-Mutated Breast Cancer Patients

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

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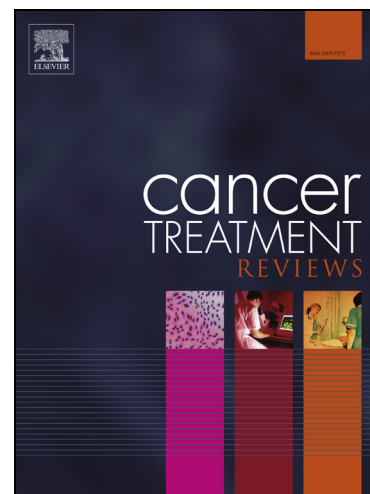
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FERTILITY AND PREGNANCY ISSUES IN *BRCA*-MUTATED BREAST CANCER PATIENTS

Matteo Lambertini^{1,2,*}, Oranite Goldrat³, Angela Toss⁴, Hatem A. Azim Jr.², Fedro A. Peccatori⁵, Michail Ignatiadis², Lucia Del Mastro⁶, Isabelle Demeestere³

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* ShareTM (<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 ≤ 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 magnitude 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.

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Disclosure

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FIGURE LEGEND

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

ACCEPTED MANUSCRIPT

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

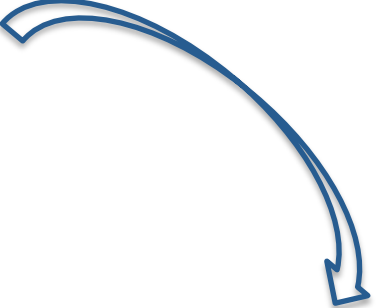
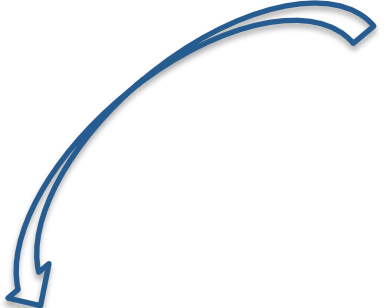
- Fertility and pregnancy-related issues are one of the main areas of concerns for young women with breast cancer.
- Carrying a germline deleterious *BRCA* mutation adds additional burden on this regard.
- Specific needs and issues should be considered when counseling *BRCA*-mutated breast cancer patients.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

BRCA1
BRCA2



Deficient DNA
repair mechanism

Genotoxic
stress



- ↓ ovarian reserve
- ↑ ovarian aging
- ↑ fertility-related problems

- ↑ risk of breast cancer
- ↑ risk of ovarian cancer
- ↑ risk of other cancers



Anticancer
treatments

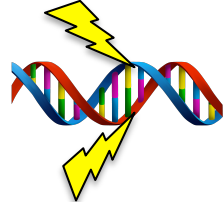


Table 1. Impact of carrying a *BRCA* mutation on reproductive potential in healthy carriers.

Author	Type of study	Number of <i>BRCA</i> 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: -Nulliparous, % -No. children (mean)	9 vs. 5; p=0.18 2.33 vs. 2.5; p=0.045	No difference
Friedman et al. 2006 [34]	Case-control study	2,828	657	Parity: -No. children (mean)	2.38 vs. 2.43	No difference
Moslehi et al. 2010 [35]	Case-control study	96	164	Parity: -Nulliparous, % -No. children (mean)	8.6 vs. 11.1 2.56 vs. 2.59	No difference
				Infertility: -Fertility medication, %	10.4 vs. 9.8	
Pal et al. 2010 [36]	Case-control study	2,254*	764*	Parity: -Nulliparous, % -No. children (mean)	23.1 vs. 24.4; p=0.54 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: -Fertility problems, % -Fertility medication, % -Fertility treatment, %	14.4 vs. 14.1; p=0.81 3.8 vs. 4.9; p=0.28 0.5 vs. 0.3; p=0.39	
Smith et al. 2012 [37]	Retrospective analysis within 2 longitudinal studies	181	2,715	Parity: -No. children (mean)	6.22 vs. 4.19; p<0.001 4.13 vs. 3.40; p=0.01	Difference favoring <i>BRCA</i> carriers
				Age at first birth (mean) years	23.44 vs. 24.18; p=0.23 23.09 vs. 24.42; p=0.004	
Finch et al. 2013 [38]	Observational study (survey)	908	908	Parity: -Nulliparous, % -No. children (mean)	31.6 vs. 33.7; p=0.35 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: -Fertility problems, % -Fertility medication, % -Fertility treatment, %	12.5 vs.13.7; p=0.46 6.0 vs. 7.0; p=0.41 0.8 vs. 2.1; p=0.04	menopause for <i>BRCA</i> carriers
Collins et al. 2013 [39]	Retrospective analysis within a prospective cohort study	819	1,021	Parity:		No difference
				-Nulliparous, %	26.5 vs. 25.1; p=0.80/p=0.28	
				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: -Fertility treatment, %	4.9 vs. 6.0; p=0.82/p=0.20	
Lin et al. 2013 [40]	Cross-sectional study	382	765	Parity:		Difference favoring non- carriers
				-Nulliparous, %	39.4 vs. 25.5; p<0.001	
				-No. children (mean)	1.3 vs. 1.5; p=0.0017	
				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:		Difference in AMH levels favoring non- carriers over <i>BRCA1</i> carriers (no difference in <i>BRCA2</i>)
				-Nulliparous, %	22/37 vs. 25; p=0.512	
				AMH level (mean) ng/ml <i>BRCA1</i> vs controls <i>BRCA2</i> vs controls	0.53 vs. 1.05; p=0.026 0.73 vs. 1.05; p=0.470	
Kwiatkowski et al. 2015 [43]	Retrospective analysis	583*	364*	Parity:		Difference favoring <i>BRCA</i> carriers
				-Nulliparous, %	9.1 vs. 16.0; p=0.003	
				-No. children (mean)	1.8 vs. 1.5; p=0.002	
				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:		Difference favoring non- carriers
				-Nulliparous, %	23.9 vs. 20.7; p=0.04	
				Age at menopause (mean) years	53 vs. 53; p=0.207 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 <i>BRCA1</i> carriers (no difference in <i>BRCA2</i>)
				Age at first birth (mean) years	24.9/25.7 vs. 25.0/25.6; p=0.76/p=0.87	
				Infertility: -Fertility treatment, %	6/5 vs. 5/7; p=0.65/p=0.64	
				AMH level <i>BRCA1</i> vs controls <i>BRCA2</i> vs controls	25% lower; p=0.02 No difference; p=0.94	
Van Tilborg et al. 2016 [46]	Cross-sectional study	124	131	Parity: -Nulliparous, %	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: -Fertility problems, % -Fertility treatment, %	30 vs. 15; p=0.03 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 <i>BRCA</i> 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 <i>BRCA1</i> carriers (no <i>BRCA2</i> included)
Oktay et al. 2010 [50]	Prospective cohort study	12	33	ART performance: -Oocyte yield (mean) No. -Poor response rate**, %	7.9 vs. 11.3; p=0.025 33.3 vs. 3.3; p=0.014	Difference favoring non-carriers over <i>BRCA1</i> carriers (no difference in <i>BRCA2</i>)
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 <i>BRCA1</i> vs controls <i>BRCA2</i> vs controls	1.22 vs. 2.23; p<0.001 1.12 vs. 2.23; p<0.001 1.39 vs. 2.23; p<0.127	AMH levels favoring non-carriers over <i>BRCA1</i> carriers (no difference in <i>BRCA2</i>)
Shapira et al. 2015 [52]	Retrospective cohort study	62*	62*	ART performance: -Oocyte yield (mean) No. -Poor response rate*, %	13.75 vs. 14.75; p=0.49 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 <i>BRCA</i> mutated breast cancer patients	Indication in <i>BRCA</i> mutated breast cancer patients
Embryo/oocyte cryopreservation	Yes (standard)	<ul style="list-style-type: none"> - Possible lower response to controlled ovarian stimulation - No data on pregnancy and fertility preservation outcomes 	Yes (standard)
Cryopreservation of ovarian tissue	Yes (experimental)	<ul style="list-style-type: none"> - High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years - No data on the efficacy and safety of the procedure (only one pregnancy reported in a <i>BRCA2</i>-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 GnRHα during chemotherapy	Yes (standard)	<ul style="list-style-type: none"> - High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years - No data on the efficacy and safety of the procedure 	To be considered only in patients diagnosed at a very young age

Abbreviation: GnRH α , gonadotrophin-releasing hormone agonists.