

# Pregnancy in breast cancer survivors: safety and feasibility

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## Abstract

**Breast cancer is the most frequent neoplasm occurring in women during their reproductive age; cancer treatments can affect, at different rates, childbearing plans.**

**Over the last decades, there has been a rising trend of delaying childbearing especially in western countries, so that more women are diagnosed with breast cancer before completing their family plans.**

**In daily clinical practice of any Oncologist dealing with breast cancer patients, there is an increasing number of patients inquiring about the feasibility and safety of pregnancy following cancer diagnosis.**

*KEY WORDS: safety, pregnancy, breast cancer.*

## Introduction

With improvements in prognosis and survival after cancer diagnosis, fertility and parenthood are important quality-of-life issues for cancer survivors, and several fertility-preserving initiatives have been launched. Fertility-preserving strategies, such as gonadal shielding during radiotherapy or cryopreservation of embryos and sperm cells, have been already introduced in the clinical practice during treatment of young patients with Hodgkin lymphoma or testicular cancer as well conservative surgery in young women with gynecological cancers at an early stage. In the last decades, different strategies have further improved post-cancer reproduction.

Parental age at first birth has increased in most populations, a trend that may also influence fertility after cancer and the total number of children among cancer survivors.

Despite fertility-preserving initiatives, post-cancer reproduction is expected to be lower than that of the general population, especially in female cancer survivors when compared with males parenthood after cancer. Pregnancy rates among female cancer survivors are 40% lower compared with the general population adjusted for age, education level and previous parity (1).

Chances of subsequent pregnancy depend on the type of cancer. Patients with melanoma or thyroid cancer have pregnancy rates similar to those in the general population; in contrast, for breast cancer survivors subsequent pregnancy is about 70% lower than the general population (Figure 1).

Due to the rising trends of delaying pregnancy to later in life, more women are diagnosed with breast cancer before completing their family plans. Therefore enquiry about the feasibility and safety of pregnancy following breast cancer is on the rise.

The purpose of this paper is to provide a comprehensive review of the literature data about safety and feasibility of pregnancy after breast cancer diagnosis and treatment. An update of the current strategies for preserving fertility in this subset of patients is provided.

## Methods

The Authors identified all relevant articles available on PubMed databases until May 2016, using as keywords: breast cancer and pregnancy, fertility preservation and cancer, ovarian toxicity, ovarian failure.

The data provided in these review have been extrapolated from well-conducted prospective and retrospective cohort studies along with systematic reviews and meta-analyses.

## Results

### **SAFETY: children and mothers**

#### *1. Birth outcome*

Little data are available about the effect of breast cancer and related treatments on birth outcome: the few studies regarding pregnancy in women after breast cancer have focused on maternal prognosis. However biological mechanisms related to the cancer or its treatments may impact fetal growth, development and

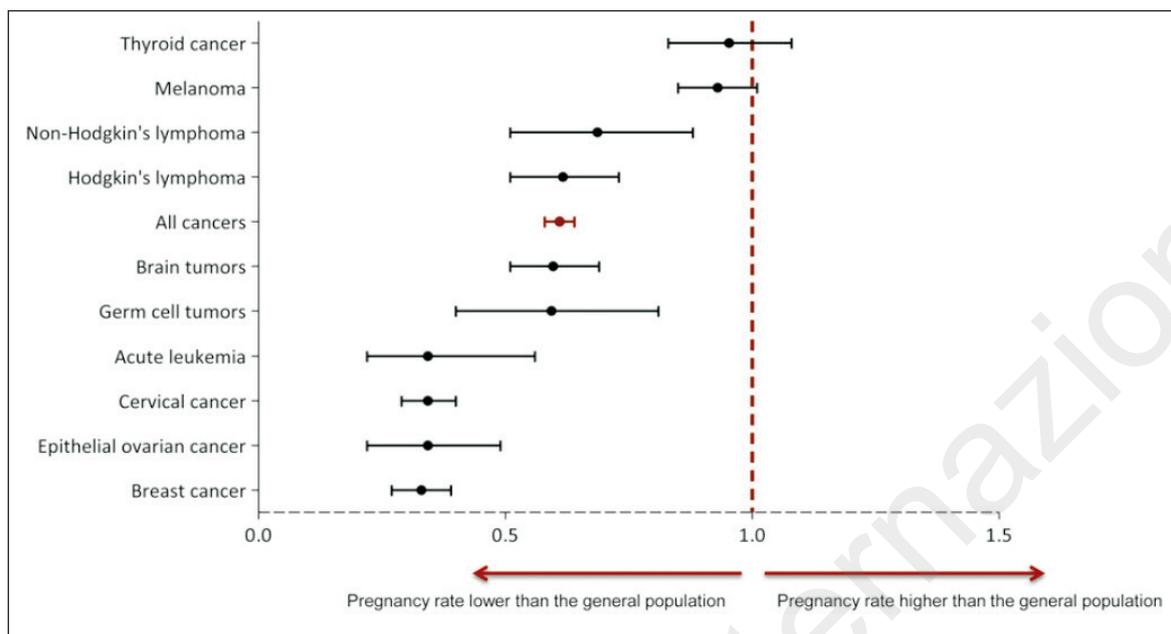


Figure 1 - Female cancer survivors have 40% less chance of becoming pregnant compared with the general population. Analysis adjusted for age, previous parity and level of education. Data taken from a population-based study from Norway, which included 16 105 female cancer survivors and 85 500 controls.

teratogenesis. Cohorts studies without control groups, including a small number of patients diagnosed with breast cancer during or shortly after pregnancy, showed that the majority of women gave birth to healthy children.

The largest study was conducted by a Danish group in 2006 which investigated whether maternal breast cancer affects birth outcome in a nationwide cohort study of women with breast cancer with respect to preterm birth, low birth weight at term, stillbirth and congenital abnormalities as well as mean birth weight (2).

The Authors identified from the Danish Cancer Registry all women who were diagnosed with breast cancer from January 1943 to December 2002, including all the patients diagnosed at any time before pregnancy, during pregnancy or until 2 years post partum. All cases classified as "carcinoma *in situ*" were excluded. 695 singleton births delivered by women were identified in the breast cancer cohort.

The comparing cohort was determined as follows: for each birth by a woman with breast cancer, 50 comparison births matched by month and year of birth, by county of mother's residence, and born to 50 different women, who were not diagnosed with any cancer before or during the pregnancy or until 2 years after the birth were selected from the Birth Registry. Altogether, 33,443 single births were selected for the comparison cohort.

In this study no excess risk of adverse birth outcome for the 216 newborns of women with breast cancer before pregnancy was evidenced. Stratification by mother's treatment did not change the results. For 37 newborns of women diagnosed during pregnancy, the prevalence ratio (PR) of preterm birth was 8.1 [95%

confidence interval (CI): 3.8-17]. However, 10 of the 12 preterm deliveries among these women were elective early deliveries. Among 442 births of women diagnosed in the 2 years from time of delivery, the PR of preterm birth was 1.4 (95% CI: 1.0-2.0), and the PR of low birth weight at term for boys was 2.9 (95% CI: 1.3-6.3), suggesting that male fetuses are more vulnerable than female. According to the Authors, the eight-fold increased odds of preterm birth for newborns of women who were diagnosed with breast cancer during pregnancy reflected a higher rate of elective early delivery, probably to allow an earlier start of cancer therapy. Overall, the results seem quite reassuring regarding the risks of adverse birth outcome for breast cancer patients.

Another study was performed in 2006 by Ives et al. in order to determine the rate of pregnancy, management, outcome of the cancer, and outcome of the first subsequent pregnancy among women who survived breast cancer (3). In 1982-2000, 2539 women aged 15-44 in Western Australia had a pathologically confirmed diagnosis of breast cancer. Of these, 123 (5%) had at least one pregnancy after their diagnosis and before 31 December 2004. In total, 175 subsequent pregnancies were confirmed in the 123 women; 45 (37%) women had more than one subsequent pregnancy. Sixty six (54%) women had a live birth. Three women successfully underwent *in vitro* fertilization treatment to conceive after their diagnosis; at follow-up they were alive and without recurrence. The median time from diagnosis to first subsequent pregnancy was 23 months. There were no still births or ectopic pregnancies. Two births occurred before 36 weeks: a set of twins at 32 weeks after spontaneous rupture of

membranes and a singleton birth by caesarean section at 30 weeks when the mother developed both local and distant metastases. All children were alive and well at last follow up. Sixty two (50%) women conceived within two years of their diagnosis. Abortion was more common when conception occurred within two years from diagnosis ( $P = 0.012$ ) and proportionally more abortions occurred in the first six months after breast cancer was diagnosed and while the woman was undergoing active treatment. There was a statistical difference in outcome of pregnancy between women who delayed conception of two years and those who conceived within two years ( $P = 0.021$ ), even if women who conceived within six months of diagnosis (that is, during most adjuvant treatment) were excluded from the analysis. The Authors conclude that their study does not support the frequent medical advice given to premenopausal women with a diagnosis of breast cancer to wait two years before attempting to conceive, even though this recommendation may be valid for women still receiving treatment (i.e. endocrine therapy) or with advanced disease at diagnosis. Further studies are needed.

### 2. Prognostic impact on mothers' survival

In 2012, the estimated age-adjusted annual incidence of breast cancer in 40 European countries was 94.2/100,000 and the mortality 23.1/100,000 (1). There is a steep age gradient, with about a quarter of breast cancers occurring before age of 50, and <5% before age of 35. The estimated 5-year prevalence of breast cancer in Europe in 2012 was 1,814,572 cases (4). Prevalence is increasing, as a consequence of increased incidence and due to improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection (5, 6). Breast cancer is the most common neoplasm among women during the reproductive age. Over the past decades, there has been an increasing number of women delaying childbearing for various reasons (7), and a large number of patients with breast cancer inquiring about fertility-related issues and whether a subsequent pregnancy could alter their risk of disease recurrence or disease-related survival.

In the past, breast cancer survivors were frequently advised against pregnancy after cancer by their physicians on the assumption that the hormonal milieu of pregnancy could induce breast cancer recurrence. Induced abortion rate was quite high, ranging from 20 to 40%, probably reflecting the uncertainties of patients and physicians regarding the safety of pregnancy following breast cancer diagnosis (8, 9). Gelber et al. reported that 23 of 33 induced abortions (69%) were recommended by the treating physician (10).

Several studies have been conducted in order to investigate the impact of pregnancy on breast cancer survival and a large meta-analysis has been published in 2011 (11). The Authors selected the studies eligible for the analyses according to the presence of a 'case' group of patients who became pregnant anytime fol-

lowing breast cancer diagnosis (irrespective of pregnancy outcome) and a 'comparator' group of breast cancer patients who did not become pregnant. The studies had to be independent from other studies to avoid giving double weight to estimates derived from the same study and had to compare outcomes in terms of OS, number of deaths, or any other way to evaluate impact on survival, providing sufficient information to estimate hazard ratio (HR) or odds ratio (OR) as measures of relative risk (RR), and 95% confidence interval (CI). 14 studies, published between 1970 and 2009, met the eligibility criteria and were included in the meta-analysis. 1244 women who became pregnant following breast cancer diagnosis were compared with a control group of 18,145 patients. Women who became pregnant following breast cancer diagnosis had a significant improvement in OS compared with those who did not become pregnant (Pooled RR: 0.59; CI: 0.50-0.70). Unfortunately, none of the studies was stratified for estrogen receptor (ER) or HER2 status. The relative risk of death of patients who became pregnant following breast cancer was remarkably lower amongst those with history of node-negative breast cancer (PRR = 0.63; 95% CI: 0.41-0.96) than those with node-positive disease (PRR = 0.96; 95% CI: 0.67-1.37).

A multicenter retrospective study was performed in order to explore the prognostic impact of pregnancy after breast cancer according to estrogen receptor status (12). A total of 333 pregnant patients and 874 matched nonpregnant patients were analyzed, of whom 686 patients had an ER-positive disease. No difference in DFS was observed between pregnant and nonpregnant patients in the ER-positive (HR 0.91; 95% CI, 0.67 to 1.24,  $P = .55$ ) or the ER-negative (HR 0.75; 95% CI, 0.51 to 1.08,  $P = .12$ ) cohorts. However, the pregnant group had better OS (HR 0.72; 95% CI, 0.54 to 0.97,  $P = 0.03$ ), with no interaction according to ER status ( $P = 0.11$ ). The Authors conclude that pregnancy is not protective against BC recurrence in women with a history of an endocrine-sensitive BC at least during the first 5 years after pregnancy. However, the results are rather reassuring for a lack of detrimental effect irrespective of ER status.

### Ovarian toxicity

Cytotoxic treatments (CT) prolong survival of patients affected by early breast cancer (EBC), even in endocrine-responsive tumors. This benefit is particularly evident in women younger than 50 years of age (13). However, CT, in a variable percentage of patients, causes iatrogenic amenorrhea (chemotherapy-related amenorrhea, CRA) or menopause (chemotherapy-related menopause, CRM).

CRA and CRM positively influence survival in patients affected by EBC, as reported in the majority of studies (14). In endocrine-responsive EBC patients both a direct cytotoxic activity and an indirect suppressive hormonal effect mediated by damage to ovarian estrogen-producing cells may explain this benefit (14, 15),

with consequent greater effectiveness of CT in younger, rather than in older patients.

Amenorrhea (defined as 'lack of menstruation for >6 months during 24 months of follow-up') related to adjuvant CT-regimens AT/TAC/AC-T in premenopausal EBC patients was evaluated in a large prospective trial. Patients with CRA had significantly better overall and disease-free survival than those without amenorrhea, regardless of treatment received and estrogen-receptor (ER) status (16, 17). However the prognostic role of CRA was found to be restricted to ER-positive patients in a subsequent 12-month landmark analysis (18). These results were consistent with data of IBCSG 13-93 and IBCSG VIII trials, where CRA was related with improved outcome only in the subgroup of ER-positive EBC patients (19, 20).

Chemotherapeutic drugs are characterized by different rates of gonadotoxicity (Tab. 1). Alkylating agents usually cause permanent and irreversible gonadal damage. Cisplatin and adriamycin modestly affect ovarian function. Otherwise, cycle-specific agents, such as methotrexate, 5-fluorouracil and vinca alkaloids are associated with mild or no gonadotoxicity. Several factors can influence the onset and the extent of ovarian toxicity, including age, type of CT regimen, dose intensity, cumulative dose of CT received, previous treatments, genetic and environmental factors, the use of tamoxifen, and also breast cancer itself.

### 1. Definitions and pathogenesis of ovarian toxicity induced by CT

Physiologically, from fetal life until menopause, there is a progressive loss of oocytes (21), and an accelerated atresia of the oocytes, approximately at the age of 37, is responsible for the mean age of physiological menopause at about 51 years (range 40-60 years) in Western countries (21-23).

Cessation of menses before the age of 45 is defined as 'early' menopause, whereas when it occurs even earlier, before the age of 40, it is called 'premature' menopause or premature ovarian failure (POF).

'Premature' is an arbitrary definition, a cut-off point designated by the World Health Organization (WHO) that corresponds to a menopause occurring at an age two standard deviations below the population mean (24).

POF induced by CT can be determined through primordial follicle depletion, impairment of follicular maturation, or both (25, 26).

Such chemotherapeutic drugs as the above mentioned alkylating agents (i.e. cyclophosphamide, ifosfamide) are most commonly associated with permanent and irreversible gonadal damage, probably because these drugs are not cell cycle-specific (27). Therefore, both resting and growing primordial follicles can be damaged by treatment that includes these agents (25, 27). It is worth noting that in the adult

**Table 1 - Risk of permanent chemotherapy related amenorrhea (CRA) from single agent and combination chemotherapy regimens. Modified from F. Torino et al. Critical Reviews in Oncology/Hematology 89 (2014) 27-42.**

	Single agent	PoliCT regimens
High risk (> 80%)	<ul style="list-style-type: none"> <li>- Cyclophosphamide</li> <li>- Ifosfamide</li> <li>- Chlorambucil</li> <li>- Melphalan,</li> <li>- busulfan</li> <li>- Nitrogen mustard</li> <li>- Procarbazine</li> <li>- Thiotepa</li> </ul>	<ul style="list-style-type: none"> <li>- CMF, FEC, FAC × 6 cycles in women aged ≥40 years</li> </ul>
Intermediate risk	<ul style="list-style-type: none"> <li>- Cisplatin</li> <li>- Carboplatin</li> <li>- Adriamycin</li> <li>- Taxanes</li> </ul>	<ul style="list-style-type: none"> <li>- CMF, FEC, FAC × 6 cycles in women aged 30-39 years</li> <li>- AC, EC × 4 in women aged ≥40 years</li> <li>- Taxane-containing combinations</li> </ul>
Low (< 20%) or absent risk	<ul style="list-style-type: none"> <li>- Bleomycin</li> <li>- Dactinomycin</li> <li>- Vincristine</li> <li>- Vinblastine</li> <li>- Methotrexate</li> <li>- Mercaptopurine</li> <li>- 5-Fluorouracil</li> <li>- Tamoxifen</li> <li>- GnRHa in women ≥ 40 years</li> </ul>	<ul style="list-style-type: none"> <li>• CMF, FEC, FAC × 6 cycles in women aged &lt;30 years</li> <li>• AC, EC × 4 in women aged &lt;40 years</li> </ul>
To be determined	<ul style="list-style-type: none"> <li>-Oxaliplatin</li> <li>- Irinotecan</li> <li>- Monoclonal antibodies (trastuzumab, bevacizumab)</li> <li>- Tirosin-kinase inhibitors (lapatinib)</li> </ul>	

ovaries over 99% of ovarian reserve is characterized by resting primordial follicles, that include oocytes at prophase of meiotic division. On the other hand, cycle-specific agents such as methotrexate, 5-fluorouracil, bleomycin and vinca alkaloids are associated with mild or no gonadotoxicity. Cisplatin and adriamycin modestly affect ovarian function.

The chemotherapy-induced ovarian damage is alike accelerated ovarian aging (26, 28, 29), resulting in a shortening of the reproductive life and premature menopause. It is characterized by reduction in the follicle pool, increased follicular apoptosis, premature atresia, harmed blood vasculature, cortical fibrosis, eventually leading to ovarian atrophy (29).

The ovaries have a fixed number of oocytes so they are extremely sensitive to various cytotoxic drugs (30). The damage induced by cytotoxic agents to the ovaries can involve both granulosa and theca cells with consequent alteration of endocrine and esocrine functions, that can result in transient amenorrhea or, in case of apoptosis of primordial follicles, can evolve in POF.

Nowadays, such damage has been mainly attributed to two mechanisms. The first, a direct mechanism, involves a reduction in the follicular pool, through the induction of apoptosis and premature atresia of oocytes, according to the "burn-out" hypothesis. This, in turn, stimulates primordial follicles to grow and replace growing follicles, reducing the primordial pool of resting follicles. The latter, an indirect mechanism, acts through a stromal injury with damage to vessels, cortical fibrosis, which wavers in the atrophy of oocytes (29).

Recently, correlations between acute vascular damage and alteration in ovarian blood flow, size, and function, associated with an abnormal hormonal profile (particularly, anti-mullerian, AMH, levels) and clinical symptoms, have been found in a small cohort of premenopausal patients with EBC treated with neoadjuvant/adjuvant CT. At the end of chemotherapy ovarian blood flow was significantly reduced and, patients treated with sequential chemotherapy experienced further blood flow decrease after the second sequence. Only patients who did not receive cyclophosphamide showed a mild alteration in ovarian blood flow (31).

This evidence may at least partially explain also the unexpected increased incidence of POF detected in women enrolled in a clinical trial evaluating bevacizumab as treatment for stage II-III colorectal cancer (32).

## 2. Clinical aspects of POF induced by CT

The risk of POF induced by CT is mainly related to patient age at the time of the beginning of treatment, type and cumulative doses of chemotherapy. Age >40 years is considered the strongest predictor of both CRA and CRM (28, 33, 34).

For some drugs, such as cyclophosphamide, a direct correlation between dose intensity and the onset of POF has been demonstrated (35).

Furthermore, poli-CT-regimens that incorporate multiple agents are generally related with more negative impact on ovarian activity, compared with monotherapy (27, 36).

How much taxanes impact of on the onset of CRA/CRM is still unclear, but the addition of taxanes has been related with a further increase of CRA rate in EBC patients (37-39).

Oligomenorrhea or temporary amenorrhea are usually secondary to a damage to both steroid-producing (granulosa and theca) cells and the oocytes of growing follicles. When the extent of the injury is associated with almost complete follicular depletion or viability of about <1000 follicles, menopause will arise.

Even if many patients > 40 years of age develop CRA, ovarian failure may be temporary in a considerable number of women. To date, the percentage of women with CRA/oligomenorrhea who will later develop CRM is yet unknown.

In a considerable number of patients, at the end of CT, the remaining follicles may still be recruited from the primordial pool. Accordingly, gonadotropin levels may return to normal values, menstrual cycles may resume and/or fertility may recover months to years after the end of chemotherapy. Menses are more likely to return in younger women, in those treated with less gonadotoxic regimens and, in any case, in those with better basal ovarian reserve (14).

However, the resumption of menses (RM) may be delayed, occurring even after 2-3 years of CRA.

Unluckily, recovery of menses is not a synonymous of fertility. Women who recover the ability to menstruate following CT, even regularly, may have a reduced likelihood of pregnancy (40, 41).

## Preserving fertility during BC treatment

The increasing complexity of integrated treatments, more effective but also more toxic, already requires, whenever planning treatment, more attention to the long-term quality of life, including a careful discussion on reproductive issues.

In this context, approaches aimed at preserving fertility in young patients affected by EBC are of particular significance. At baseline, and in the subsequent follow-up, the clinician should pay particular attention on potential ovarian toxicity of the chemotherapeutic treatment and offer all available strategies aimed at preserving fertility and/or ovarian function.

Several options, standard and experimental, are now available for younger BC patients wishing to preserve their fertility potential from damage of CT (42). Adjuvant chemotherapy is usually initiated within 4-6 weeks after surgery, therefore the clinician may introduce patients early towards fertility preservation strategies.

Available methods include cryopreservation techniques and/or the administration of GnRH-agonists (43, 44). However, each of these methods presents advantages and disadvantages. Methods based on cryopreservation are costly, complex, and have a significant failure rate (45, 46), particularly in patients > 40 years of age (47). Both embryo and oocyte preservation techniques require ovarian stimulation before harvest, which exposes patients to high estrogen lev-

Table 2 - Main available options for fertility preservation in breast cancer patients. Modified from N. Tomasi-Cont et al. The Breast 23 (2014) 503- 510. Abbr. GnRHα: Gonadotropin-releasing hormone analogs; OF: ovarian function; OS: ovarian stimulation.

Strategy	Definition	Experimental or standard strategy	Ovarian Stimulation (OS) required	Delay in the initiation of chemotherapy	Surgery	Preservation of ovarian function (OF)	Available in all centers	Observations
Oocyte cryopreservation	Harvesting and freezing of unfertilized eggs	Standard	Yes	Yes	Yes	No	No	OS lasts 10-14 days
Embryo cryopreservation	Harvesting eggs, <i>in vitro</i> fertilization, and freezing of embryos	Standard	Yes	Yes	Yes	No	No*	Consolidated; Partner required; *It varies by country. No available in Italy (L.40/2004)
Ovarian tissue cryopreservation	Freezing of ovarian tissue and re-implantation after cancer treatment	Experimental	No	No	Yes	Yes**	No	Not applicable if high risk of ovarian involvement; 40 births in literature; **No data on the longterm OF.
Ovarian suppression GnRHα	Use of hormonal therapies to protect ovarian tissue during chemotherapy	Experimental	No	No	No	Yes***	Yes	Therapy carried out before with and during CT; Simple and not expensive *** Few data on long-term recovery and maintenance of OF

els, a potential risk in patients with ER+BC. Alternative approaches of ovarian stimulation with the use of letrozole (48) or tamoxifen (49) have been developed for EBC patients, with promising results on the quality of the oocytes and embryos collected.

In addition, surgery induces a delay of 2-6 weeks in starting CT. New protocols with ovarian stimulation started sooner, in the luteal or late follicular phases, have been developed with preliminary promising results in terms of oocyte collection (50, 51).

Ovarian tissue cryopreservation is an experimental option for fertility preservation (52, 53). This strategy does not require any stimulation or delay in the start of CT. It may preserve fertility and ovarian hormonal function. However, the costs and the need of at least two surgical procedures (removal and then reimplantation of ovarian tissue) may represent a disadvantage.

Moreover, an accurate histological analysis of ovarian biopsy samples before reimplantation is mandatory for the potential risk of reintroducing malignant cells (52). Following reimplantation of ovarian tissue, gonadal function is expected to be restored within 3-6 months, but, nowadays, no data on the longterm recovery are available (54, 55). To date, about 40 live births have been reported in the literature after reimplantation of cryopreserved ovarian tissue (56).

Pharmacological preservation of the ovaries with the use of GnRH analogs during chemotherapy is an attractive option to preserve gonadal function and fertility. The use of GnRH analogs has some advantages: it is simple to administer, cheap and available in all centers; CT need not to be delayed, and a male partner is not required.

GnRH agonists must be administered one week to six months before CT and continue until the end of CT. However, safety of the use of GnRH agonists in BC cancer patients has been questioned. The POEMS phase III trial demonstrated that concurrent administration of goserelin with chemotherapy appeared to protect against ovarian failure, reducing the risk of early menopause and improving fertility in hormone-receptor-negative breast cancer (57). The PROMISE-GIM6 phase III randomized study showed that the use of triptorelin-induced temporary ovarian suppression, during CT in premenopausal patients with EBC, reduced the occurrence of treatment-related early menopause (OR = 0.28; 95% CI, 0.14-0.59; P < .001), and increased number of pregnancies (58). No differences in the 5-year disease-free survival (DFS) between treatment arms were observed (83.7% in CT alone arm vs 80.5% in CT plus LHRHa: HR=1.17; 95% CI 0.72-1.92, p=0.519) in both hormone receptor-negative and positive patients (59).

All the above mentioned techniques are not mutually exclusive. The concomitant use of GnRH agonists for ovarian suppression with cryopreservation techniques increases the chances of preserving fertility in young women (44).

Table 2 shows synthetically the characteristics of all of these approaches.

## Discussion and conclusions

Breast cancer is the most frequently occurring cancer in women of reproductive age. The available anti-cancer treatments have improved survival in young patients with early breast cancer, but both chemotherapy and endocrine therapy can cause acute and chronic side effects, including gonadal toxicity. Due to the trend to delay family plannings, especially in western countries, fertility preservation is becoming a main issue in the treatment of breast cancer when diagnosed in young women.

Therefore oncofertility counseling becomes a key moment in the decision-making process of young patients who are interested in future fertility (42).

A recent retrospective study (61) has evaluated whether patients had a documented fertility discussion (FD) with their oncology physician prior to therapy, what options were chosen, and if pregnancy was achieved. The Authors reviewed data of 303 women aged <40 years who were diagnosed breast cancer from 2006 to 2014 and treated with chemotherapy and/or endocrine therapy. Patient demographics, treatment regimens, presence or absence of FD, *in vitro* fertilization (IVF) consultation, GnRH agonist use, and subsequent successful pregnancy were analyzed. Although not every woman in this group desired pregnancy, 89% women having a documented FD sought further fertility consultation and options. 20% women were prescribed a GnRH agonist only for ovarian protection during chemotherapy, 63% underwent IVF consultation only, and 6% had both a GnRH agonist prescribed and an IVF consultation. The overall pregnancy rate was 7% at a mean of 3 years post breast cancer treatment. Pregnancy after treatment was more common among those pursuing IVF consultation or prescribed a GnRH agonist.

Little is known about how fertility concerns affect treatment decisions or fertility preservation strategies at the time of initial cancer diagnosis. As part of a prospective study, Ruddy et al. have investigated fertility concern and preservation items among 620 women with newly diagnosed early-stage breast cancer at age <40 years: 68% of patients discussed fertility issues with their physicians before starting therapy, and 51% were concerned about becoming infertile after treatment (62). Because of concerns about fertility, 1% of patients chose not to receive chemotherapy, 2% chose one chemotherapy regimen over another, 1% considered not receiving endocrine therapy, 3% decided not to receive endocrine therapy, and 11% considered receiving endocrine therapy for less than 5 years; 10% used fertility preservation strategies. Greater concern about fertility was associated with younger age, nonwhite race, not having children, and receipt of chemotherapy. The Authors conclude that many young women with newly diagnosed breast cancer have concerns about fertility, and for some, these substantially affect their treatment decisions; moreover only a minority of women currently pursue available fertility preservation strategies in this setting.

Nowadays, the knowledge of menopausal status of a

patient with endocrine-responsive EBC in CRA is of utmost importance not only in order to provide accurate evaluation on residual fertility, but also in prescribing the most suitable endocrine therapy (i.e., tamoxifen or aromatase inhibitors, AI). AI as single agents are contraindicated in premenopausal patients and in women presenting residual ovarian function (63).

In recent years a new medical discipline, named “oncofertility”, is emerging: all the oncologists dealing with young patients in reproductive age should be aware of the available fertility preservation strategies and prepared to discuss with the patients the gonadal toxicity of the proposed anticancer treatment and their family plannings.

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