Breast Cancer, Fertility Preservation and Reproduction

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Springer

Pregnancy After Breast Cancer

6

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Introduction

eiving cancer diagnosis can be devastating for many patients but thanks to ances in cancer therapies it is not a death sentence anymore. Cancer survival rates increasing and life after cancer is a real chance for many patients worldwide. In ope, about one third of cancer patients have a relative 5-year survival rate greater 80 % [1]. Similar survival rates are seen in the United States, Canada and tralia. Lower survival rates in developing countries are most likely due to late nosis and limited availability of up-to-date standard treatments [2, 3].

n Italy, every day about 30 new cases of cancer are diagnosed in patients below ge of 40 years and many of them are women with breast cancer. About 10 % of st cancer diagnosis occurs in patients younger than 40 years [4].

reast cancer in young women is frequently more aggressive than tumours diag- d in older women. Often metastases at loco-regional lymph nodes are detected agnosis and biological and molecular characteristics identify phenotypes at prognosis [5]. As a consequence, systemic treatments in addition to local ther- re frequently recommended. In spite of this, poorer survival rates and higher f recurrence are reported in these subgroup of patients [6].

anks to adjuvant therapies, overall and disease-free survival are improving ime and most of the patients long survive to breast cancer. Chemotherapy and rine therapy extend time to recurrence but, on the other hand, bring about short- and long-term side effects. Among them, ovarian failure with ture menopause is particularly relevant to young women. In the last few years,

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ger International Publishing Switzerland 2015
a, F.A. Peccatori (eds.), *Breast Cancer, Fertility Preservation*
roduction, DOI 10.1007/978-3-319-17278-1_6

a trend towards delaying pregnancy to later in life has been observed and many women receive a diagnosis of breast cancer before completing their families [7]. In Italy, the frequency of pregnancy in women aged 35 years or more was 12 % in 1990, 16 % in 1996 and it is estimated that will amount to 25 % in 2025 [4]. Diagnosis and treatment of breast cancer often threaten fertility. Guidelines highlight the importance of discussing with patients the gonadotoxic effect of antineoplastic treatments and the risk of fertility loss as well as the available fertility preservation strategies, in addition to the chances of future conception, pregnancy and breastfeeding [8, 9].

An internet-based survey reports that more than 50 % of women at the time of diagnosis of breast cancer have fertility concerns [10], but less than 10 % of women with previous breast cancer subsequently become pregnant. This is around half the pregnancy rate seen in age-matched group without breast cancer [11]. Several studies showed that fertility counselling remains inadequate and lacks of a standardised approach [12]. The fear that pregnancy after breast cancer could worsen the prognosis does interfere with the reproductive desire of young women and impairs future conception.

There is increasing evidence in favour of the feasibility and the safety of pregnancy and breastfeeding after breast cancer; therefore, women with a history of successfully treated breast neoplasm should be given the possibility to conceive and get mother.

6.2 The Relationship Between Breast Cancer and Pregnancy

Many scientific evidences link pregnancy and risk of breast cancer. Several epidemiological studies showed a protective effect of pregnancy against breast cancer. The protection does not take place immediately: for a few years after pregnancy there is a transient increase of breast cancer incidence. This dual effect of pregnancy on breast cancer incidence, with an increased risk for about 5–10 years after a pregnancy, followed by a lifelong protective effect, was described in a large population-based study from Norway. This study reported an increase of breast cancer incidence lasting 3 years after a full-term pregnancy, followed by long-term reduction of risk [13].

Another Norwegian registry-based study investigated the relationship between breast cancer prognosis and reproductive factors among 16,970 parous women with invasive breast tumour [14]. Analysing the relationship between parity, age and breast cancer outcome, it was observed that when diagnosis occurs before the age of 50 years, survival is worse in women with high parity compared with those with low parity. This is likely due to a combination of genetic factors, molecular characteristics of breast tumours in young patients and hormonal milieu. No clear-cut association was observed between parity and breast cancer survival when diagnosis occurs in women who were 50 years or older.

Several studies tried to explain this time-dependent effect of pregnancy on breast cancer risk. Molecular studies linked postnatal mammary involution process with

susceptibility to neoplastic evolution. It is hypothesised that angiogenesis, alteration of extracellular matrix and inflammatory process are involved in this mechanism. The stroma of the mammary gland is greatly modified depending on endocrine status and reproductive factors. Post-lactational tissue remodelling may provide a break in the natural stromal barriers that suppress tumour cell motility and invasion with increased risk of tumour progression [15]. Another hypothesis involves mammary stem cells. In mouse models, it was observed that mammary stem cells are highly responsive to steroid hormone signalling, despite their ER and PgR phenotypes. Following pregnancy, it was registered a transient increase in the number of mammary stem cells, which may indicate a cellular basis for the short-term increase in breast cancer risk [16].

Pregnancy-related hormonal changes seem to be involved particularly in the long-term protective effect. Preclinical models demonstrated that high doses of estradiol induce apoptosis in long-term deprived, ER-positive breast cancer cell lines [17]. Activation of caspases via the Fas/Fal pathway appears to be involved in the promotion of apoptosis due to estradiol. The long-term oestrogen deprivation seems to sensitise breast cells to estradiol pro-apoptotic effect, with a reduction of number and growth of cancer cells in vitro. Response to estradiol depends on the ER subtypes expressed by the cells. Breast cells expressing ER-β undergo apoptosis, whereas cells expressing ER-α are protected from apoptosis. A comparative study analysed the oestrogen receptor (ER) expression in nulliparous and parous women. Compared to nulliparous women, a lower expression of ER-α and a higher expression of ER-ß was observed in parous women [18]. Other authors suggested the fetal antigen hypothesis. Clinical studies found that a high percentage of parous women, but not nulliparous women, show evidence of immunisation to antigens located on breast cancer cells. Fetal cells and breast cancer cells share common antigens: the immune response exerted by maternal immunity against fetal cells may be extended against cancer cells [19].

6.3 Pregnancy After Breast Cancer

Several case-control and population-based studies have been performed with the aim of understanding the prognostic impact of pregnancy after breast cancer. None of these studies demonstrated a negative impact of a subsequent pregnancy [20]. In particular, a meta-analysis was performed to investigate the impact of pregnancy on overall survival of women with previous breast cancer [21]. Fourteen studies were included in the meta-analysis, with a total number of 1,244 patients who became pregnant after breast cancer and 18,145 patients who did not. It was observed that women who became pregnant after adequate treatments for breast cancer had a statistically significant improvement in overall survival as compared to the control group [pooled relative risk (PRR): 0.59; confidence interval (CI): 0.50–0.70]. Analysing each study singularly, 8 studies reported a significant survival advantage for subsequent pregnancy, whilst the remaining 6 studies showed a not statistically significant trend in favour of pregnancy.

Studying the impact of pregnancy on prognosis, the "healthy mother effect" must be kept in mind. This is a relatively old concept introduced by Sankila in 1994, to explain a potential confounding factor in the interpretation of the observed effect of pregnancy in women with cancer [22]. It expresses the possibility that those women who got pregnant after breast cancer are a subgroup of patients free of relapse and healthier than the others. This could introduce a selection bias: women who become pregnant after breast cancer have better survival because they belong to a subgroup of patients with good prognosis, independently and not because of a protective effect of the pregnancy.

In the previously cited meta-analysis, a subgroup analysis in order to overcome this bias was performed. The outcome of women with pregnancy after breast cancer was compared with the outcome of controls who were known to be free of relapse. A not statistically significant trend favouring pregnancy after breast cancer was still observed [21]. Even if selection bias may partially contribute to the risk of death reduction, it seems still reasonable to conclude that pregnancy is safe in women with a history of breast cancer and does not increase the risk of recurrence.

In spite of this, a possible negative impact of pregnancy on breast cancer prognosis, particularly in patients with endocrine-responsive tumour, is still of concern. Recently, a study with the aim of investigating the effect of pregnancy in women with breast cancer according to oestrogen receptor status was conducted by Azim et al. [23]. In the three subgroups (oestrogen receptor-positive cohort, oestrogen receptor-negative cohort and all patients) no difference in disease-free survival was observed between women who become pregnant and those who did not conceive. Further, the pregnant group had better overall survival, again with no interaction observed according to ER status [23]. In summary, the study indicates that pregnancy is not protective against a relapse in patients with endocrine-sensitive tumour, but at the same time it does not exert a detrimental effect.

A further point of discussion is the time interval between the end of antineoplastic treatments and pregnancy. Several studies analysed this relationship with inconsistent results. A significant survival improvement was observed only for women who conceive after 24 months or more (Table 6.1). A not significant protection was

Table 6.1 Cox's proportional hazard model for survival in women with breast cancer with time-dependent variable stratified by time from diagnosis

Time to subsequent pregnancy (months)	Beta coefficient	*P* value	Hazard ratio (95 % CI)
<6	0.79	0.579	2.20 (0.14–35.42)
6–24	−0.80	0.135	0.45 (0.16–1.28)
>24	−0.74	0.009	0.48 (0.27–0.83)

(Each stratified model adjusted for age, lymph node status, and tumor size)
Modified from Ives A. et al. Pregnancy after breast cancer: population-based study. BMJ 2007;334:194

observed for women who delayed pregnancy for at least 6 months [24]. A large population-based study corroborates the theory that the risk of dying decreases with increasing the gap between diagnosis and childbirth [25].

The optimal timing of pregnancy after breast cancer is still undefined and the decision depends on patient's prognosis, age and personal condition. Because of the reassuring studies on patients who get pregnant 2 years and more after breast cancer and the observation that recurrences occur more frequently in the first few years, a delay of 2–3 years is conventionally recommended.

This time interval would also allow to recover from chemotherapy-induced ovarian toxicity. Women with ER-negative breast cancer should be advised to wait at least 6 months from the end of treatments before conceiving, to avoid the possible toxic effect of chemotherapy on growing oocytes.

As to ER-positive breast cancer, current guidelines recommend at least 5 years of endocrine therapy [26]. Furthermore, recent evidence suggests that 10 years of tamoxifen confer even greater protection [27]. Because of the teratogenetic effects of tamoxifen, pregnancy during endocrine therapy is contraindicated and an off-therapy period of 3–6 months is recommended before conceiving. But the reproductive potential is declining year by year, because of the physiological loss of ovarian reserve and the harms of chemotherapy. The feasibility of a temporary break of the hormonal therapy allowing to conceive and have a full-term pregnancy, with subsequent completion of endocrine treatment is under investigation. A prospective study of the Breast International Group and North American Breast Cancer Group (BIG-NABCG) is currently ongoing, investigating the clinical and biological features contributing to a safe and successful pregnancy in ER-positive breast cancer patients. The analysis will focus on both oncological outcomes (local and distant recurrences and survival) and obstetrical outcomes (spontaneous abortion, preterm delivery, intrauterine growth restriction, low weight at birth, fetal malformations). Secondary endpoints of the study are the feasibility and the impact of a temporary break of endocrine therapy to allow conception and the optimal duration of subsequent hormonal therapy after delivery and breastfeeding [28].

6.4 Obstetrical and Neonatal Outcome

One of the unnamed concerns that patients face is the fear of a potential teratogenic effect of antineoplastic treatments on the offspring. Few data are available on birth outcomes in breast cancer survival; however, no excess risk for the newborn health is suggested [28].

Some studies found a higher rate of abortion than in general population. This information may be biased because most of the studies did not discriminate between spontaneous and induced abortion. When this issue was considered, the risk of spontaneous abortion did not seem to be higher in breast cancer patients than in general population. On the contrary, the rate of induced abortion is consistently higher, suggesting that uncertainties of patients and physicians about safety of pregnancy after breast cancer often lead to dramatic choices [29]. Studies comparing

disease-free survival in patients who completed their pregnancy to term and patients who had an abortion found a not statistically significant trend towards better outcome in women who had a full-term pregnancy [23].

Two large studies assessed the obstetrical and neonatal outcomes of pregnancies following breast cancer. A Danish nationwide cohort study investigated whether maternal breast cancer affects birth outcome [30]. Data about pregnancies of 216 women with a history of breast cancer were matched with a comparison cohort of 10,453 women belonging to general population. Similar rates of low birth weight, stillbirth and congenital abnormalities were observed in the two groups. A small and not statistically significant higher preterm delivery rate was observed in the breast cancer cohort. Mean birth weight was nearly 3,400 g in both groups, as well as mean gestational age at delivery. Different findings were reported in a Swedish cohort study aiming to assess delivery risk and neonatal health [31]. Data were extrapolated from the Swedish Medical Birth Registry and the Swedish Cancer Registry, including 331 mothers with a history of breast cancer and 2,870,518 mothers belonging to general population. An increased risk of delivery complication, caesarean section, preterm delivery and congenital malformations and no difference in low birth weight rate at delivery was observed. Authors conclusion is that pregnancy after breast cancer should be considered at high risk and therefore managed and surveilled accordingly.

Usually women with previous breast cancer are more likely to give birth at an older age than the general population. Both studies point out this difference in maternal age. About 50 % of women in breast cancer cohort are 35 years old or more at delivery, with a mean age of 34 years, whereas in the comparison group the figures are 11 % and 28 years, respectively [30, 31]. It is well known that pregnancy at an old age is more susceptible to many comorbidities and complications as gestational hypertension, preeclampsia, gestational diabetes and other conditions that bring about high risk for pregnancy outcome and require special surveillance. This may partially explain the slightly higher rate of pregnancy complications reported in the Swedish study, but uncertainties still exists.

6.5 Breastfeeding After Breast Cancer

Many factors, such as personal, cultural, social and environmental factors, influence women's decision about breastfeeding. Beyond these, breast cancer survivors face unique physical and emotional factors that might impact their decision and ability to breastfeed.

A qualitative research explored by an interview the experience and the feelings about breastfeeding in a selected group of breast cancer survivors [32]. Generally, patients alleged the wish to breastfeed, but also anxiety and concerns about doing it. This highlights the need of prenatal education and information to prepare the prospective mother to the challenges of breastfeeding. Breast cancer survivors alleged physical and emotional problems, mainly because they had to rely primarily or entirely on one breast. Treatments for breast cancer can affect lactation. Proximity of

he surgical incision to the nipple-areola complex, dose and type of radiation therapy nay reduce or inhibit lactation. Thus, many patients can breastfeed from the untreated reast only, with consequent uncertainty about whether or not the milk supply would e sufficient for the infant [32]. Failure to nurse from one breast should not affect the se of the other and the mother should be reassured about the adequacy of milk pro-luction by a single breast, sufficient for the nutritional need of the newborn.

Another survey analysis was performed investigating the breastfeeding patterns nd habits in breast cancer survivors [33]. Hypoplasia and hypotrophia of the oper-ted and irradiated breast were observed, with consequent reduced milk production, ipple pain, physical changes and discomfort during latching. Furthermore, a previ-us mastectomy was associated with short-lasting breastfeeding. This is not only ustified by the fact that these patients have a single breast to nurse their babies, but lso women with previous breast conserving surgery used one breast only for lacta-ion. A possible alternative explanation is that body image plays an important role n the success of breastfeeding, and breast-conserving surgery, in spite of mastec-omy, may reinforce the feeling of maternal adequacy. A proper breastfeeding coun-elling is a key factor for successful and prolonged breastfeeding in breast cancer urvivors. This experience often brings about a psychological rehabilitation and atients express satisfaction to have been able to breastfed their babies, even if it equired efforts and sometimes milk supplement.

These results enlighten the reasons of breast cancer survivors to breastfeed and he challenges which they will face and concern them. It is of the utmost importance hat physicians provide practical and continuous support to the mother, especially luring the postpartum period.

Beyond feasibility the safety of breastfeeding after breast cancer treatment emains an open question. Several studies have demonstrated the protective effect of reastfeeding on breast cancer risk in general population. A meta-analysis including data from 47 epidemiological studies, evaluating the relationship between breast-eeding and breast cancer, has demonstrated a 4.3 % reduction of the relative risk of reast cancer for each year that a woman breastfeeds [34]. In order to reduce biases, tratifications for age, parity, ethnicity and age at first delivery were performed, natching women who breastfed and who did not breastfeed on the basis of the same haracteristics. The conclusion was that the benefits are statistically significant and reastfeeding should be encouraged.

While there is evidence that breastfeeding reduces breast cancer incidence in general population, there are no solid epidemiological data about breastfeeding after breast cancer. A retrospective case-control study investigated the survival rate of patients treated for breast cancer who subsequently became pregnant [35]. A ecent re-analysis of those data was performed, specifically focused on the role of reastfeeding. A better survival was suggested in women who breastfed. These data could be biased, but it may be supposed that breastfeeding does not have a detrimen-al effect on breast cancer outcome [36].

The mechanisms underneath the association of breastfeeding and reduction of reast cancer incidence are not known. Several hypotheses were expressed in vari-us studies and were synthesised in a review article [36]. Some data suggest that

lactation may reduce the carcinogens level in the breast. Another hypothesis is the suckling-related blockage of the hypothalamus-pituitary axis leading to lactational amenorrhoea. From animal models, it was hypothesised that differentiation of the mammary gland as observed during pregnancy and lactation protects from neoplastic evolution. The role of prolactine has been widely studied but with conflicting results, and the impact of this hormone on initiation and promotion of breast cancer in humans remains unclear.

Epithelium changes and stromal activation which occur in remodelling breast tissue may be associated with a temporary increase in breast cancer incidence. This observation recommends a thorough follow-up of women with history of breast cancer after pregnancy or lactation. Patients and physicians often tell of the fear of a delay in diagnosis in case of tumour recurrence. Lactation does not interfere with clinical and radiological evaluation of the breasts. Ultrasound exam can be safely performed and in case of suspicion, mammography or breast magnetic resonance imaging can be performed after having drained the lactating breasts [36].

Despite uncertainty, the benefits of breastfeeding to the baby and the mother are well established. Newborns who are breastfed are protected from infections in the short period and are less susceptible to develop autoimmune diseases and metabolic disorders at adult age. Furthermore, a benefit in neurocognitive development of the baby breastfed has been suggested. Breastfeeding bears several advantages for the mother as well. Women who breastfeed have better control of postpartum bleeding, return swiftly at the usual weight and are heavily gratified by the emotional bond which is created with her baby.

In conclusion, current evidence suggests that breast cancer survivors who wish to breastfeed, should be encouraged and supported in their efforts.

6.6 Childbearing Attitudes of Young Breast Cancer Survivors

Many studies have shown that pregnancy and parenthood are two important issues for young women with breast cancer. As breast cancer-related mortality declines, the impact of anticancer treatments on reproductive potential is getting more relevant, and fertility impairment may worsen the quality of life in a growing number of patients. For some young breast cancer survivors, the threat to their childbearing plans has major emotional and psychological consequences. Literature and clinical practice demonstrate that some women remain fertile and have a spontaneous pregnancy after a history of cancer. Additionally, the advent of advanced assisted reproductive technology within the oncology field has made fertility preservation an option for women, prior to the initiation of treatments. As known, other options are available for infertile women, such as adoption and third-party reproduction, but most couples crave biological offspring.

Several studies showed that the risk of early menopause and infertility are causes of concern for about the half of young women who receive breast cancer diagnosis. Some patients reported that this fear conditioned treatment decisions [37]. Infertility

in cancer patients is associated, more frequently than in general population, to anxiety, depressive symptoms and sexual impairment which have a negative impact on the quality of life.

But even when fertility is preserved, other concerns upset breast cancer patients. Women fear that the child might be born with a birth defect because of the chemotherapeutic agents they received. They are anxious about a shorter life expectancy and are afraid of having not enough energies to raise children. Furthermore, women feared that the offspring would have a greater susceptibility to cancer [38].

On the other hand, some patients perceive the benefits that could be achieved by having children after breast cancer treatment. Raising a child can be a powerful motivator to stay alive and healthy, it may strengthen the relationship with the partner, it brings back normalcy in their life and it would restore the sense of femininity and sexuality [39]. Breast cancer survivors who are disease-free often feel healthy enough to consider a pregnancy. This is called a reasonable wellness, which may express the ethical guide into the difficult choice of getting mother.

In clinical practice, gynaecologists and oncologists are frequently faced with the issue of educating women about childbearing after breast cancer. However, some studies suggested that these professionals often feel discomfort and lack of knowledge about how to best educate women with cancer-related fertility matters, leaving women's fertility concerns poorly addressed. Attending physicians may perceive the fertility preservation as a low priority issue, compared with the treatment of cancer or they could fear that fertility preservation techniques may dwindle the efficacy of anticancer treatments. Presently, there are guidelines stressing the need to communicate with and educate young patients regarding fertility issues. Oncologists should refer interested and appropriate patients to reproductive specialists as early as possible, to allow a rapid access to fertility preservation strategies and to avoid delaying the chemotherapy onset [8, 9].

6.7 Breast Cancer, Pregnancy and Breastfeeding in BRCA1/2 Mutation Carriers

Reproductive factors influence the risk of breast cancer in the general population, but few data are available in the selected group of women with mutations in BRCA1 and BRCA2 genes. BRCA1 and BRCA2 are tumour suppressor genes which are involved in multiple processes, including DNA damage repair and recombination, and regulate normal cell differentiation. During pregnancy and breastfeeding, breast cells divide and differentiate; thus, it could be supposed that reproductive factors have different impacts on breast cancer risk in the BRCA mutation carriers and in general population.

A large retrospective cohort study including women carrying BRCA1/2 mutations investigated the impact of pregnancy on breast cancer incidence [40]. No difference was found between parous and nulliparous women, and the same results were observed in BRCA1 and BRCA2 mutation carriers. It does not appear that

parity per se influences the risk of breast cancer in this particular subgroup of women.

Inconsistent results are reported about the association between breastfeeding and breast cancer risk. Some evidences suggest a protective effects of breastfeeding, even stronger than in general population, but only among BRCA1 mutation carriers [41, 42].

It is known that hereditary breast cancer is different from sporadic tumour and differences are observed between breast cancer patients with BRCA1 and BRCA2 mutations as well. This might suggest that the biological pathway for carcinogenesis is different for these two genes.

Our knowledge about the impact of pregnancy after breast cancer in BRCA1/2 mutation carriers is even poorer. This is partly due to the small proportion of women carrying mutations in these genes. The question is sensible, because of the typical early age of onset of hereditary breast cancer. A multicenter, case-control study which included women known to carry a BRCA 1 or BRCA 2 mutation and history of breast cancer has been published recently [43]. The cases were patients with pregnancy-associated breast cancer or pregnancy following breast cancer. The controls were selected among patients who did not get pregnant after breast cancer diagnosis and who were alive and recurrence-free at the time of the delivery of the baby in the matched group, in order to reduce potential confounding bias, such as the healthy mother effect. The 15-year survival was excellent in the two groups, around 90 %, and no significant difference was observed between cases and controls after adjustment for several prognostic factors. Despite the limitations of the study, first of all the small sample size, these results are encouraging and future research is recommended to prove the not detrimental effect of pregnancy after breast cancer in this particular subgroup of women [43].

There is an issue in BRCA1/2 mutation carriers that deserves special consideration. Some studies suggested that the deficient DNA repair mechanism due to mutations in BRCA 1 and BRCA 2 genes may make oocytes more susceptible to DNA-damaging agents. Furthermore, it has been speculated that BRCA mutation carriers may have a lesser ovarian reserve than general population and undergo premature menopause. As a consequence, BRCA mutation carriers may be more susceptible to chemotherapy-induced gonadotoxicity with severe ovarian reserve loss [44]. Diagnosis of breast cancer in a young patient with BRCA mutation raises concerns about her future fertility. A trend towards earlier referral to fertility specialists underscores the importance of this issue. However, the better approach in this particular group of patients is not an easy choice. On one side data suggest a poor response to ovarian stimulation for oocyte retrieval and cryopreservation, particularly in BRCA1 mutation carriers; on the other side ovarian tissue cryopreservation for BRCA mutation carrier is disputed because of the risk of ovarian cancer and lastly the efficacy of temporary ovarian suppression with GnRH agonists is still controversial [44].

All these findings suggest that BRCA mutation carriers may have a shorter reproductive life, and this should be taken into account in the management of young breast cancer patients who desire a future pregnancy. Whether or not the low ovarian reserve and poor response to ovarian stimulation may reduce the fertility potential of women with BRCA mutations is still unknown and further research is needed.

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