

Is it prudent to consent to or recommend pregnancy in breast cancer survivors?

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ABSTRACT

Background: Female breast cancer survivors and some health professionals may have doubts about the advisability of pregnancy after breast cancer. Such doubts concern possible recurrences, increased mortality, and adverse effects on the newborn.

Purpose: The aim of this report is to present the case of a woman who, after 48 months of breast cancer survival, wished to start a pregnancy. A further aim is to indicate whether it is prudent to consent to or to recommend pregnancy after a breast cancer diagnosis.

Case report: This report concerns a patient without satisfied parity, who, at the age of 36 years, presented left breast carcinoma with negative nodes: estrogen receptors in less than 2% of the studied cells and negative progesterone receptors. She received surgical management, chemotherapy and radiotherapy. At 48 months of survival, she wished to start a new pregnancy. On requesting a risk/benefit recommendation from her treating doctors, she did not obtain a unanimous position. By her own decision, she sought and achieved a spontaneous pregnancy, which led to a live birth. Five years later, her child shows normal growth.

Conclusion: Evidence suggests increased survival in mothers with a breast cancer history and subsequent pregnancy. Despite being high-risk pregnancies due to the increased possibility of low birth weight, preterm delivery, and small fetus for gestational age, studies suggest that pregnancy may be consented to or recommended in breast cancer survivors.

KEYWORDS

Breast neoplasms, survival, cancer survivors, pregnancy.

Introduction

When considering the statistics of neoplastic diseases worldwide, breast cancer is found to have the highest incidence, followed by lung and colorectal cancer^[1]. Breast cancer is present both in developed and in developing countries. Screening, early diagnosis, prompt treatment, and follow-up of the disease are all crucial. According to the Global Cancer Observatory (GLOBOCAN), 2,088,849 new cases of breast cancer occurred worldwide in 2018^[2]. For the same year, in Latin America and the Caribbean, the incidence was 27%, that is, more than 462,000 cases, according to the Pan American Health Organization^[3]. Meanwhile, for 2019, the American Society of Clinical Oncology (ASCO) estimated 325,010 breast cancer cases in the United States, including in situ and invasive cancers^[4]. The Spanish Association Against Cancer reported 33,307 new cases in 2019^[5]. In Colombia, an increase from 7,000 cases in 2012 to 13,380 in 2018 has been observed^[2,6].

The highest mortality rates from cancer are attributed to lung, colorectal and stomach cancer, while breast cancer in women is in fifth place^[1,2]. In 2018, there were 626,679 deaths from breast cancer worldwide, most frequently in Western Europe, East Asia and North Africa, with 169,640, 119,678 and 53,917, respectively^[2,5]. In Latin America and the Caribbean,

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14,097 deaths were identified, of which 3,702 occurred in Colombia^[2].

Health care measures have reduced mortality and increased the rate of breast cancer survival^[3,5], with survivors recovering productivity and returning to social and family interactions. More than 80% of women with early diagnosed breast cancer become over-10-year survivors^[7]. Several variables influence survival: age, comorbidities, tumor extension, clinical stage at the time of diagnosis, time to the beginning of therapy, and presence of access barriers to health care, among others^[4,8]. 12% lower five-year survival has been reported in women who had a delay of three months between diagnosis and the beginning of treatment, while 7% lower survival was recorded in those with delays of between three and six months^[9]. Over the same number of years, 99% survival can be expected if the tumor is localized, 85% if it is regional, and 27% when there is

distant invasion^[4].

In addition, an increasing number of young women diagnosed with breast cancer have not yet completed their family^[10]. Kopeika *et al.*^[7] report that approximately 20% of localized or invasive breast cancers are diagnosed before menopause; the same was indicated by Del Mastro *et al.*^[11]. There is uncertainty about the impact of the disease and its treatment on ovarian reserve or future reproduction, and about the impact of pregnancy on the survivor's health^[12,13]. The aim of this report is to present the case of a woman who, after 48 months of breast cancer survival, wished to carry a pregnancy, and also to indicate whether it is prudent to consent to or recommend pregnancy after a breast cancer diagnosis.

Case report

This report concerns a 46-year-old patient, Hispanic, physical therapist, living in Cartagena, Colombia. She had menarche at 12 years of age. Obstetric history: two pregnancies that ended by cesarean section and none miscarriages, both children born at term and exclusively breastfed until six months.

At 36 years of age, she perceived a mass in her left breast, associated with a burning sensation. On physical examination, the following were found: symmetrical breasts and a nodule of 1.6 centimeters in diameter in the lower left quadrant of the left breast, close to the submammary sulcus. Additionally, an elongated hardened area was palpated in the ipsilateral external superior quadrant. No lymphadenopathy, secretions or skin changes were identified. Breast ultrasound showed a homogeneous mass with a solid appearance. Mammography showed a heterogeneous fibroglandular mammary parenchyma, dense appearance of fatty tissue, and a spiculated nodular image. It was classified as BIRADS-V. Breast biopsy was performed and poorly differentiated infiltrating ductal carcinoma, nuclear grade-3 and equivocal test (2+) for the HER2/neu oncogene was identified.

Left breast quadrantectomy was performed, removing a firm, irregular, whitish mass measuring 2.5x2.0x3.0 cm. Sentinel node biopsy of the axillary region was performed. The histopathological report showed: "cells with abundant eosinophilic cytoplasm, nuclei with marked pleomorphism, vesicular, prominent nucleolus, and abundant atypical mitoses, arranged in a syncytial pattern, in solid nests. Stroma with moderate lymphocytic infiltrate, formation of cords and trabeculae with areas of necrosis and lymphovascular invasion". The sentinel node study described: "follicular and sinusoidal hyperplasia, negative for malignancy". The pathological diagnosis was: "infiltrating, atypical medullary carcinoma with lymphovascular invasion". The pathological staging was T2N0M0, and the clinical staging IIA. Fluorescent *in situ* hybridization test (FISH) was positive for amplification of the HER2/neu oncogene. Immunohistochemical reaction showed: estrogen receptors in less than 2%, negative progesterone receptors and KI67 in 90% of all studied cells.

Thirty radiotherapy sessions, six anthracycline cycles, four paclitaxel cycles and one year of trastuzumab were performed. In addition, the left breast was esthetically reconstructed with

transposition of the right abdominal rectum. During that period, family planning was based on fertility awareness-based and barrier methods. There were no changes in the frequency, duration or amount of menstrual bleeding during the course of the treatment or in the following three years.

At 41 years of age, with 48 months of breast cancer survival, the patient expressed the wish to have a new pregnancy. Treating gynecologists considered a new pregnancy neither opportune nor prudent, while her oncologists did not consider a new pregnancy to be risky. The patient, by her own decision, suspended family planning and, three months later, noticed a menstrual delay. On physical examination, a large, irregular, nodular uterus was found. hCG was positive, and on ultrasound an eight-week gestational sac with a live embryo plus multiple uterine fibroids were observed. Pregnancy was uneventful and ended at term, with a healthy newborn, who, at five years old, has shown normal growth and development.

At 120 months of survival, the patient has normal imaging follow-up and the tumor markers have been negative for recurrences. She has been asymptomatic, although in the last year she presented a right cervical nodule close to the jugular vein. A biopsy was performed and was negative for tumor cells.

Discussion

Worldwide there is an increasing trend to delay motherhood until the end of the third or beginning of the fourth decade of life^[10,12]. This is consistent with an increase in the incidence of breast cancer in women who have not yet completed their family. In a series of Mexican survivors of breast cancer, 64.2% were nulliparous at the time of diagnosis^[12]. Therefore, it is common for the desire for fertility to persist after the end of the treatment^[10,13,14]. More than 45% of breast cancer survivors want to become pregnant^[7].

There are several possible scenarios, since the reproductive impact of the treatment is not always predictable. In one of them, adjuvant therapy, which includes radiotherapy, chemotherapy or anti-estrogens, can cause gonadal cytotoxicity with apoptosis of ovarian germ cells^[11,15]. Irregularity or absence of menstrual cycles, alteration in endocrine markers of integrity of the hypothalamic-pituitary-ovarian axis, early ovarian failure due to iatrogenic follicular depletion, early menopause, and subfertility are reported^[10,16]. In these situations, assisted reproduction techniques with ovodonation will be required^[11,15]. Goldrat *et al.*^[17] observed no difference in rates of pregnancy, spontaneous or by assisted reproductive techniques, in breast cancer survivors.

In a second scenario, treatment-induced amenorrhea is temporary, depending on the drugs and doses used, and the patient's age and organic conditions. Those under 35 years tend to achieve future fertility, facilitated by their increased ovarian reserve^[7,12]. After breast cancer, the chance of achieving pregnancy with a live newborn is approximately 8% in women under 35 years of age and 3% in those aged 35-45 years^[11]. Different ovulation induction schemes are available depending on the integrity of the ovarian cycles, but in some cases, spontaneous pregnancy is possible.

In a third scenario, menstrual cycles are not compromised and spontaneous pregnancies may occur [10,12,14,15,18], as happened in the patient described in this case report, who showed no changes in endocrinological reproductive function with the different oncological interventions performed.

When health professionals, without distinction of specialty, are asked for an opinion or counseling by breast cancer survivors who want to achieve pregnancy, they will usually show some doubt or lack clear arguments [13,19]. Some of them, as well as the community in general, tend to mistakenly believe that pregnancy can be associated with breast cancer recurrence [7], however available clinical data do not show that women who become pregnant after a breast cancer diagnosis have a worse prognosis than those who do not [11,20]. Frequently, obstetricians and gynecologist have to respond if they consent to spontaneous pregnancy or if hormonal therapeutic tools or assisted

reproduction techniques are needed to achieve it. Table 1 presents data that can be used to weigh up whether it is prudent to consent to or recommend pregnancy in breast cancer survivors.

The initial concern of survivors and their families is the risk/benefit relationship of a new pregnancy for the woman's health. It is a general cause of distress when the tumor expresses estrogenic receptors (+), since it is thought that high hormonal levels derived from pregnancy could induce cancer cell proliferation, tumor growth, recurrence and spread. However, several authors [13,18] indicate that lower expression of alpha estrogenic receptors, progesterone and HER2 can be expected in women who became pregnant after breast cancer compared with women who did not, so pregnancy could provide a protective effect in breast cancer survivors with estrogen receptors (+). In this subgroup of women, pregnancy can be consented after they have received adjuvant endocrine therapy, which is

Table 1 Pregnancy in breast cancer survivors.

AUTHOR	OBJECTIVE	DESIGN	POPULATION	RESULTS	COMMENTARY
Azim et al. 2011 [13]	To investigate the effect of pregnancy on overall survival of women with a history of breast cancer diagnosis.	Meta-analysis. Fourteen studies: retrospective control-matched (seven); population-based (four); hospital-based (three) Pooled relative risk (PRR) was estimated.	1,244 cases 18,145 controls.	Women who became pregnant following breast cancer diagnosis had a significant improvement in overall survival compared with those who did not become pregnant. PRR: 0.59 [95% CI: 0.50-0.70] Q test for heterogeneity $p=0.04$; $I^2=43.1$. Subgroup analysis according to the type of study Case-controls: PRR: 0.52 [95% CI: 0.40-0.68] Q test for heterogeneity $p=0.24$; $I^2=24.8$. Population-based PRR: 0.74 [95% CI: 0.56-0.99] Q test for heterogeneity $p=0.71$; $I^2=0$. Hospital-based PRR: 0.48 [95% CI: 0.26-0.88] Q test for heterogeneity $p=0.16$; $I^2=45.7$. Impact of pregnancy on overall survival according to nodal status Negative. PRR: 0.63 [95% CI 0.41-0.96] Q test for heterogeneity $p=0.75$; $I^2=0$. Positive. PRR: 0.96 [95% CI: 0.67-1.37] Q test for Heterogeneity $p=0.28$; $I^2=20.8$.	That pregnancy is safe in women with a history of breast cancer. Thus, counseling against pregnancy in these women remains unjustified.
Rippy et al. 2009 [16]	To investigate the effect of breast cancer, its treatment and counseling on future pregnancy and fertility.	Eligible patients were identified through a database from the Royal Surrey County Hospital breast unit. UK. A questionnaire was sent to all patients asking about pregnancy, counseling and fertility issues, as well as terminations and miscarriage rates after breast cancer.	263 patients.	The questionnaire response rate was 66%. 39 women had wanted children before diagnosis, and 24 still wanted them post treatment, giving a successful pregnancy rate of 75%. Eighteen patients became pregnant, four with more than one pregnancy. Of the 18 patients identified, 17 had live births, and one patient had an abortion due to concerns about fetal damage. Overall known mortality from breast cancer in the entire post-breast cancer cohort studied was 9.5% over five years. The mortality due to breast cancer was 10% in non-pregnant patients and 6% in patients who became pregnant after breast cancer.	Pregnancy after breast cancer does not confer a poor prognosis. A higher rate of pregnancy than expected was found after treatment, possibly due to newer treatments including fertility preservation.
Nye L et al. 2017 [18]	To investigate breast cancer-free survival in premenopausal women diagnosed with hormone receptor-positive breast cancer who became pregnant within five years of diagnosis of breast cancer.	Cohort retrospective analysis. Using the Northwestern Medicine Enterprise Data Warehouse, this was a joint initiative across the Northwestern University Feinberg School of Medicine and Northwestern Memorial Healthcare Corporation. Chicago. USA.	32 premenopausal women with a diagnosis of estrogen receptor-positive breast cancer and subsequent pregnancy within five years. The control cohort included 29 women matched for age and stage of breast cancer who had not become pregnant.	Of the 32 women in the pregnancy cohort and 29 women in the control cohort, 19 (63%) and 23 (82%) had received endocrine therapy. Four women (14%) in the control cohort experienced breast cancer recurrence compared with 8 women (26%) in the pregnancy cohort ($p=0.34$). The 5-year disease-free survival rate was 92% [95%CI: 81-100] in the control cohort compared with 84% [95%CI: 72-97] in the pregnancy cohort. The difference was not statistically significant ($p=0.69$).	Did not demonstrate poorer disease-free survival for premenopausal women with estrogen receptor-positive breast cancer who became pregnant within 5 years of diagnosis.

AUTHOR	OBJECTIVE	DESIGN	POPULATION	RESULTS	COMMENTARY
Ives et al. 2006 [14]	To identify women who survived breast cancer and subsequently conceived and to determine the rate of pregnancy (proportion), management, outcome of the cancer, and outcome of the first subsequent pregnancy.	Population-based descriptive study with cases identified from the Western Australian data linkage system and validated by review of medical charts. Supplementary data obtained from hospital and clinician records.	123 women aged < 45 with a diagnosis of breast cancer who subsequently conceived.	104 patients (85%) who had a pregnancy after cancer reported as alive with a median follow-up of 128 months. Overall survival at five years 92% [95% CI: 87-97]. Overall survival at ten years 86% [95% CI: 80-93]. Overall survival at five and ten years from the first pregnancy was 87% [95% CI: 81-93] and 85% [95% CI: 78-91], respectively. Abortion was more common when conception occurred within the first two years, p=0.012. Especially if it was within the first six months after diagnosis. Pregnancy after two years improved overall survival. HR: 0.59 [95% CI: 0.37-0.95], p=0.03. When we stratified the proportional hazard regression model by time from diagnosis, subsequent pregnancy improved overall survival in those women who waited 24 months to become pregnant HR: 0.48 [95% CI: 0.27-0.83], p=0.009. Lymph node positive HR: 2.61 [95% CI: 2.17-3.13], p=<0.001.	For women with localized disease and good prognosis, conception six months after treatment is unlikely to reduce survival. Pregnancy is unlikely to compromise the survival prospects for women treated for breast cancer who have tumors with good prognosis. Women are currently advised to wait at least two years after treatment for breast cancer before conception. Women who survive breast cancer and who conceive > 24 months after diagnosis have similar or better survival than other women with breast cancer.
Blakely et al. 2004 [24]	To assess the effect of pregnancy on the subsequent risk of recurrence after treatment for breast carcinoma.	Retrospective cohort of diagnosed patients between 1974 and 1998, treated for breast carcinoma with adjuvant chemotherapy at The University of Texas M.D. Anderson Cancer Center, Houston, USA.	370 survivors. 47 (13%) became pregnant and 323 (87%) did not become pregnant after treatment for breast carcinoma. After receiving chemotherapy, 203 (53%) patients resumed normal menstrual cycles and 44 (11%) became amenorrheic.	Patients who experienced a pregnancy tended to have earlier-stage disease (Stage I/II: 80% vs. 73%), fewer than four positive lymph nodes (87% vs. 52%), more estrogen receptor negativity (68% vs. 58%), and age under 30 years (57% vs. 32%) compared with patients who did not. The incidence of disease recurrence was 23% for women who experienced a pregnancy and 54% for women who did not. The women who got pregnant had earlier-stage disease, fewer positive lymph nodes, estrogen-receptor-negative tumors, and were younger than those who did not get pregnant. Disease recurrence in patients with post-treatment pregnancy HR: 0.71 [95% CI: 0.25-1.95], p=0.49. (HR <1.0 indicates a reduced risk of disease recurrence).	In the current study population, pregnancy was not associated with an increased risk of disease recurrence or poorer survival in patients previously treated for breast carcinoma. There appears to be a higher rate of miscarriage among women treated for breast carcinoma. There is no reason to discourage women who have been treated for breast carcinoma from having children if that is their choice.
Dalberg et al. 2006 [25]	To assess the risk of adverse birth outcomes in women previously treated for invasive breast cancer compared with the general population of mothers.	A population-based, cohort study from Sweden. ORs were adjusted for continuous age, year of delivery, and parity.	331 first births following breast cancer surgery, with a mean time to pregnancy of 37 months (7-163), were identified using linkage with the Swedish Cancer Registry. 2,870,932 singleton births registered in the Swedish Medical Birth Registry (1973-2002).	Births in women survivors of breast cancer were associated with: Increased risk of labor complications aOR: 1.5 [95% CI: 1.2-1.9]. Increased need for caesarean section aOR: 1.3 [95% CI: 1.0-1.7]. Increased external preterm delivery or before 32 weeks 3.20 (1.70-6.03) aOR: 3.20 [95% CI: 1.70-6.03]. Increased external preterm delivery (33-36 weeks) aOR: 1.53 [95% CI: 1.02-2.29]. Low birth weight gain below 1500 grams aOR: 2.86 [95% CI: 1.41-5.78]. Increased risk of congenital malformations aOR: 1.68 [95% CI: 1.11-2.54]. Increased birth trauma aOR: 0.58 [95% CI: 0.26-1.30]. No increase in stillbirths aOR: 1.17 (95% CI: 0.30-4.71). Neonatal mortality (first 7 days after birth) aOR: 1.83 (95% CI: 0.46-7.37). No increased bleeding in pregnancy aOR: 1.32 (95% CI: 0.49-3.56).	Pregnancies in previously treated breast cancer patients should be considered as higher risk pregnancies. Proper handling and vigilance, counseling and the closest accompaniment are important.

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Anderson et al. 2018 ^[21]	To examine the incidence of live birth and the prevalence of adverse birth outcomes according to tumor and treatment characteristics among adolescents and young adults with breast cancer.	A population-based, cohort study. Women diagnosed with breast cancer at ages 15-39 years (2000-2013) were identified using the North Carolina Central Cancer Registry, USA. The breast cancer cohort was followed until live birth, death, age 46 y, or December 2014, whichever occurred first. HRs were adjusted for continuous age PR (prevalence ratio).	338 children born to mothers with breast cancer were identified. For each birth to mothers surviving breast cancer, the authors sampled 20 births in mothers who had not had breast cancer (adjusted for maternal age and year of birth).	293 women had at least one live birth after diagnosis. The cumulative incidence of live births after breast cancer was 8% at 10 years. Births were less common among women treated with chemotherapy. Preterm (<37 weeks) Births to ER (+) breast cancer survivors, 10% Births to ER (-) breast cancer survivors, 18% Low birth weight (<2500 g) Births to ER (+) breast cancer survivors, 3% Births to ER (-) breast cancer survivors, 20% Small for gestational age Births to ER (+) breast cancer survivors, 7% Births to ER (-) breast cancer survivors, 13% Increased preterm delivery in ER (-) PR: 1.84 [95% CI: 1.11-3.06]. Probability of having children compared to women 30-34 years at the time of diagnosis 17-19 years, HR: 1.83 [95% CI: 1.40-2.39]. 35-39 years, HR: 0.19 [95% CI: 0.14-0.25]. Probability of having a child compared to localized disease Regional disease, HR: 0.54 [95% CI: 0.41-0.70] Distant disease, HR: 0.27 [95% CI: 0.09-0.84] The proportions of preterm birth, low birth weight, small for gestational age and cesarean delivery, were similar for women with and without a breast cancer history.	The findings emphasize the importance of fertility counseling. Strategies should be proposed and used to preserve fertility in young adult or adolescent patients with breast cancer. The findings suggest that the risk of adverse birth outcomes is not very high compared to women without cancer. The higher prevalence of preterm delivery among women with ER (-) breast cancer warrants greater vigilance. No significance was observed in the prevalence ratio of the proportions of preterm birth, low birth weight, small for gestational age and cesarean delivery; they were similar for women with and without a breast cancer history.
Ramírez-Torres et al. 2010 ^[12]	To evaluate the frequency of women that experienced a later pregnancy after treatment of cancer.	Retrospective, descriptive study (1994-2008), case series type. Gynecology Oncology Service. National Medical Center La Raza. Mexican Institute of Social Security. Mexico.	14 surviving breast cancer patients who became pregnant after diagnosis.	Age of the women studied: 30.1 ± 5.2 [24-40] years. 64.2% were nulliparous at the time of breast cancer diagnosis. In 50% of the cases the term pregnancy occurred in the first two years, a third was later than two years after the end of the cancer treatment. Age at which women conceived: 31.5 ± 5 [27-41]. In 14 patients there were 16 pregnancies; nine (56.2%) born at term, three preterm (18.7%) and four abortions (25.0%). The time from cancer diagnosis to the first pregnancy: 21.4 ± 11.9 mo [9-48]. The weight of term babies: 3.045 grams [2,050-3,800]. There were no phenotypic malformations or neurophysiological abnormalities in the newborns.	Although the pregnancy rate is low in the first two years after treatment, the patient can become pregnant. The study is a description of a small sample of cases.
Del Mastro et al. 2006 ^[11]	To review the incidence of pregnancy in breast cancer survivors and to identify the risks of menopause induced by chemotherapy regimens.	Narrative review.	=	The percentage of patients who have full-term pregnancies after the diagnosis of breast cancer is very small. Under 35 years: 8%, Under 45 years: 3%. The frequency of spontaneous abortions is higher than in controls without previous breast cancer, RR: 1.7 [95% CI: 1.1-2.8]. CEF regimen for six cycles (cyclophosphamide 600 mg / m ² , epirubicin 60 mg / m ² and fluorouracil 600 mg / m ²) cumulative dose, induces iatrogenic menopause: 60%. CEF regimen for six cycles (cyclophosphamide 75 mg / m ² orally day 1-14, epirubicin 60 mg / m ² IV day 1-8 and fluorouracil 500 mg / m ² IV day 1-8), induces iatrogenic menopause 51%. CAT regimen (docetaxel, doxorubicin, cyclophosphamide) induces iatrogenic menopause: 62%. Tamoxifen in addition to chemotherapy significantly and slightly increases the induction of iatrogenic menopause. There is no standard treatment to prevent induction iatrogenic of menopause by chemotherapy.	Pregnancy after breast cancer usually does not affect the prognosis of the survivor. Chemotherapy regimens can induce iatrogenic menopause. Cryopreservation of oocytes or embryos and LH-RH analogs, are promising alternatives to preserve ovarian function.

AUTHOR	OBJECTIVE	DESIGN	POPULATION	RESULTS	COMMENTARY
Kopeika et al. 2019 ^[7]	To assess fertility outcome in relation to intent to conceive in patients who had completed breast cancer treatment.	Retrospective study. Between 2011-2013, female breast cancer survivors who were under the age of 43 at the time of diagnosis, filled out a questionnaire about intent to conceive and pregnancy outcomes.	175 women survivors of breast cancer.	Age at diagnosis: 37 [25-42]. Years of survival: 6 [1-21]. 29% childless before diagnosis. 41% wanted to have more children. 17% reached pregnancy, half led to live births, 22% miscarried. 12 unwanted pregnancies, three (25%) reached the end with live births. Among those who did not wish to conceive, only 36/111 (32%) reported using contraceptives.	The study emphasizes the need for health professionals to provide contraceptive counseling to women who do not want to conceive.
Goldrat et al. 2015 ^[17]	To evaluate the impact of assisted reproductive technology on pregnancy and long-term outcomes of young breast cancer survivors.	Multi-center retrospective study in which women who were diagnosed with breast cancer (2000-2009) and had a pregnancy following breast cancer diagnosis. Five European Oncological and Fertility Centers and the Danish Breast Cancer Cooperative Group.	206 patients were evaluated. The cohort was divided into two. (A) 180 had spontaneous pregnancies. (B) 26 had pregnancies by assisted reproductive technology (ovulation induction, intrauterine insemination, <i>in vitro</i> fertilization, ICSI and egg donation).	180 patients conceived spontaneously and had a total of 256 pregnancies; 26 patients conceived with assisted reproductive technology and had 36 pregnancies. There were no differences in type of histological grade, tumor size, estrogen receptors and cancer therapy. Time from diagnosis to pregnancy: 42 months average. The time between conception and the last follow-up of the cancer was 63 and 50 months in the spontaneous and assisted reproductive technology groups, respectively. Term pregnancies: 77% and 76% in the spontaneous group and assisted reproductive technology group, respectively. No differences were observed in live births ($p=0.24$) and no difference was observed in new cancer-related events ($p=0.54$).	Pregnancy achieved with assisted reproductive technology in surviving women with breast cancer was feasible and was not detrimental in terms of the cancer outcome.
Iqbal et al. 2017 ^[20]	To compare the overall survival of women diagnosed with breast cancer during pregnancy or in the postpartum period with that of women who had breast cancer but did not become pregnant.	This population-based, retrospective cohort study linked health administrative databases in Ontario, Canada, from 2003 to 2014. The Cox proportional hazards regression model was used to estimate the HR.	7553 women aged 20 to 45 years at the time of diagnosis with invasive breast cancer.	Age at diagnosis 39.1 [20-44] years. Five-year actuarial survival rate for women without pregnancy, HR: 87.5% [95% CI: 86.5-88.4], for women with pregnancy before breast cancer, HR: 85.3% [95% CI: 82.8-87.8%] and for women with pregnancy after breast cancer, HR: 82.1% [95% CI: 78.3-85.9]. ($p>0.05$). Five-year actuarial survival rate for women who had a pregnancy six months or more after diagnosis of breast cancer, HR: 96.7% [95% CI: 94.1-99.3] and for women without pregnancy, HR: 87.5% [95% CI: 86.5-88.4]. ($p<.001$).	Pregnancy did not negatively affect the survival of women who had had breast cancer. Among breast cancer survivors who wanted to conceive, the risk of death was lower if the pregnancy occurred six months or more after the diagnosis was made.
Biglia et al. 2015 ^[19]	To present results of an online survey conducted through the Delphi technique among Italian oncologists dealing with breast cancer.	Web-based platform with 19 statements answered by 162 oncologists who expressed opinions about fertility issues and fertility preservation techniques in young breast cancer patients based on the Delphi method.	One hundred and sixty-two panelists	91% considered it important to discuss fertility issues. 86% of panelists favored the concomitant administration of GnRHa and chemotherapy 83% and 33% feared that estrogens could stimulate the growth of hidden ER+ and ER- cancer cells, respectively. 54% believed that pregnancy does not affect the prognosis of breast cancer patient More than 80% of oncologists thought that a successful pregnancy could be obtained after breast cancer. 40% expressed the view that when pregnancy occurs in the first 2 years after diagnosis, the risk of relapse increases. 60% of oncologists disagreed that fetal malformations in pregnancies after breast cancer occur in a higher percentage.	Strong consensus about discussion with patients on fertility preservation issues even if they did not raise the topic. No consensus regarding safety of pregnancy after breast cancer.

usually tamoxifen for between 5 and 10 years ^[18,21]. However, breast cancer may recur several years after primary therapy. Little is known about cancer cell biology in the survival stage, also called tumor latency. The estrogen receptor, the progesterone receptor, the receptor for human epidermal growth factor 2 (HER2), and the proliferation marker Ki-67 have been used for many years. They are used with the intent of predicting tumor prognosis and guiding therapy. Joensuu *et al.* point out that large tumor size and HER2 positivity are risk factors for rapid tumor recurrence, furthermore, positivity of the Ki-67 marker with a cut-off point of 14% was associated with early

recurrence ^[22]. The applicability of tumor markers has been reinforced by the availability of genomic classification; DNA microarray profiles allow the identification of some breast cancer subtypes ^[23]. More studies are needed to help evaluate the interrelationship between tumor markers, genetic considerations, and survivor's safety in a subsequent pregnancy.

It has been observed that long-term survival of patients who become pregnant after breast cancer is usually the same as or even longer than that of those who do not become pregnant. Also, survival is favored when conception occurs after 24 months from the diagnosis ^[14,19]. The patient described in the

present report sought pregnancy 48 months after diagnosis. The frequency of spontaneous abortions is higher when pregnancy occurs in the first two years after diagnosis or during active treatment [24]. Another reason to avoid seeking pregnancy in the first two years is the greater possibility of recurrence [10]. In a meta-analysis of fourteen studies, Azim *et al.* [13] argue that this can be explained by breast remodeling during pregnancy, which increases angiogenesis, inflammation and extracellular matrix alterations, with stimulating effects on residual cancer cells, which previously were under therapy.

Rippy *et al.* [16], in a cohort of breast cancer survivors, found lower mortality at 60 months among those who became pregnant compared with those who did not, 6% and 10%, respectively. One of the hypotheses advanced to explain this better prognosis is the “healthy mother effect”, which indicates that women who usually achieve pregnancy are those with early-stage tumors, early diagnosis, timely treatment, adequate psychosocial support, high self-esteem, high resilience, better prognosis, and no recurrences [11,14]. The present patient had all these elements in her personal, medical and family history. She was always aware of the inherent risks of pregnancy after the age of 40 years, but persisted in her desire for pregnancy. She also has a family and social support network.

Likewise, the fetal antigen theory, also known as alloimmunization, suggests the existence of protective immunization during pregnancy with antigens in fetal cells [13]. Fetal cells and breast cancer cells share common antigens, and there may be an immune response [13]. Additionally, it has been indicated that the decrease in estrogen levels at the end of pregnancy could induce apoptosis of abnormal mammary cells [18]. Igal *et al.* [20] found that five years after the diagnosis of breast cancer, the survival rate was 96.7% among women who became pregnant, compared to 87.5% among those who did not. With the aforementioned indications, there seems to be no reason to forbid or discourage the desire for pregnancy [16,18,20]. However, there are not many pronouncements that recommend seeking pregnancy in order to improve or increase survival in women who have had breast cancer.

Biglia *et al.* carried out an expert consensus survey based on the Delphi methodology Italian oncologists to determine their opinion on aspects related to fertility in breast cancer survivors. 54% of oncologists agreed that pregnancy does not affect the prognosis of patients with breast cancer, while 49% reported that an increase in estrogen levels can stimulate growth of tumor cells. There was no consensus regarding opinions and recommendations on pregnancy. In clinical practice, too, there are discordant positions among specialists, as occurred in the case report presented. On the other hand, there was consensus among experts regarding the importance of breastfeeding and of discussing, with patients, the different ways of preserving fertility before cancer treatment [19].

Another concern frequently reported by survivors is the possibility of fetal or neonatal repercussions of oncological interventions [7,11]. In this regard, the most serious, and fortunately less frequent, are fetal congenital malformations. These can occur in 7% of cases, when the first trimester of pregnancy is concomitant with chemotherapy [15,25]. To reduce this risk, administration of folic acid prior to conception is suggested or,

starting chemotherapy after the first trimester. The occurrence of fetal congenital malformations when pregnancy begins after completion of chemotherapy or radiotherapy treatment has not been documented [7,12,25].

Preterm delivery, low birth weight, small fetuses for gestational age, and cesarean delivery have been reported frequently in pregnant survivors of breast cancer [15,25]. However, Anderson *et al.* [21], in a cohort study based on data from North American populations, found that the proportions of these four outcomes were similar for women with and without a history of breast cancer. Kasum *et al.* [10] indicated that abortion rates can be high, up to 29%, and that preterm deliveries with low birth weight can reach 40%. One consequence of radiotherapy is usually a decrease in the production of breast milk by the irradiated breast, due to atrophy of breast lobes [10,19]. No adverse outcomes or sequelae have been reported in newborns of breast cancer survivors [13].

It is important that health professionals, regardless of specialty, who monitor breast cancer survivors of reproductive age offer solid preconception counseling [7,16]. The important aspects to consider include: the patient’s age, the survival time, the treatment received, the time since completion, the tumor extension, tumor markers, and the presence of hormone receptors. Therefore, counseling should be individualized and aimed at achieving appropriate decision making. Several studies [14,16,17,18,20,21,24,25] and a meta-analysis [13] have emphasized that pregnancy is safe in breast cancer survivors.

If there is no reproductive desire, or if cancer therapy is ongoing, extensive contraceptive counseling should be provided. One study found that 66% of survivors did not use contraceptive methods, half of them did not want a pregnancy, and in turn 40% reported having regular menstrual cycles [7]. Recommendations should always be based on the medical eligibility criteria and suggesting methods with greater contraceptive efficacy. The opposite occurred with the patient on this case report, who used strategies with the greatest possibility of failure.

When diagnosing breast cancer in women of reproductive age, with or without children, it is important to establish whether they want to have children in the future [4,7,13,16,21]. Since a low pregnancy rate (3-8%) after breast cancer has been reported, and the probability of spontaneous abortions is high (over 20%) [11], patients should be sufficiently informed of the different options for fertility preservation that can be used before starting oncology therapy. Administration of luteinizing hormone-releasing hormone analogs, oocyte or embryo vitrification, and ovarian tissue cryopreservation are widely proposed alternatives [4,10,13,15,16,17,21]. Information in this regard was not provided to the patient whose case is described herein.

It is recommended, as routine practice, always to ask breast cancer survivors of reproductive age about fertility desire and family planning [7]. A multidisciplinary approach at the time of cancer diagnosis, involving gynecologists and oncologists, is important to offer optimal information on fertility preservation and future pregnancy possibilities [11,15]. The desire for pregnancy in breast cancer survivors should not be discouraged. However, further research on fertility and pregnancy are needed to adequately meet the requirements of female breast cancer survivors in the reproductive stage of life.

Conclusion

Important evidence indicates that it is safe to allow pregnancy, or to carry out interventions to achieve it, in breast cancer survivors. However, an individualized approach, taking into account the single patient's personal conditions and oncological evolution, will always be necessary.

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