



FERTILITY AND PREGNANCY AFTER BREAST CANCER TREATMENT: EVIDENCE-BASED ANSWERS TO THE MAIN QUESTIONS THAT PATIENTS ASK

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ABSTRACT: *An increasing trend toward delayed childbearing for professional, personal, and socioeconomic reasons has been recently described. Accordingly, breast cancer incidence in women who have not yet completed their family is growing, with a steady mortality reduction due to improved diagnostic and therapeutic procedures.*

Breast cancer survivors have many concerns about conceiving after breast cancer, but recent literature is globally reassuring and the historical contraindication to pregnancy in patients with previous history of breast cancer should be dropped out. Miscarriages and pregnancy complications are not increased in breast cancer survivors and breastfeeding is safe and feasible.

All patients with newly diagnosed breast cancer should receive information about fertility and pregnancy issues, but not all physicians are ready to face this task.

Here we provide evidence-based answers to the main questions breast cancer patients may ask.

KEY WORDS: *Breast cancer, Fertility, Abortion, Obstetric outcome, Lactation.*

INTRODUCTION

The incidence of breast cancer with distant involvement in women from 25 to 39 year-old has increased in USA from 1.53 per 100,000 in 1976, to 2.90 per 100,000 in 2009. This is an absolute difference of 1.37 per 100,000, representing an average compounded increase of 2.07% per year over the 34-year interval¹. There is an increased breast

cancer risk with advancing maternal age at first childbirth: women with an estimated first birth median age of 41 years have a relative risk of 3.7 compared with those with an estimated first birth age of 23 years².

The reduced fertility derived from gonadotoxic therapy, the long duration of the endocrine therapy and the unjustified fears related to a negative impact of pregnancy on the evolution of breast can-

cer explain why these patients have the lowest pregnancy rate among cancer survivors. The proportion of patients with at least one full-term pregnancy after breast cancer diagnosis is only 3% for women younger than 45 years and 8% for women aged less than 35 years³. The possible adverse obstetric outcome could be a further reason⁴.

Since the historical contraindication to pregnancy in patients with previous history of breast cancer should be considered permanently dropped out, all patients with newly diagnosed breast cancer patients should receive information about their fertility and future pregnancy. An active counseling and a positive attitude of the breast team towards pregnancy may help reduce the fear of pregnancy and consequently also reduce the elective abortion rate after cancer⁵. Here, we will try to give evidence-based answers to the main questions and fears patients may ask, in order to help physicians involved in the care of young cancer patients that are interested in becoming pregnant after breast cancer treatment⁶.

METHODS

Pubmed database was searched with the following strategy:

((breast[ti] AND CANCER[TI]) OR "Breast Neoplasms"[Mesh]) AND ("Fertility"[Mesh] OR "Infertility/prevention and control"[Mesh] OR "Reproductive Techniques, Assisted"[Mesh] OR "Fertility Preservation"[Mesh] OR fertil*[ti]) AND (ITA[LA] OR eng[la])) NOT (letter[pt] OR africa[mh] OR asia[mh]). All relevant papers were read by one of the authors (LDP) and conclusions were incorporated and discussed within the text.

Is pregnancy after breast cancer safe?

In the past, pregnancy after breast cancer was contraindicated on the basis of purely theoretical assumptions, even though the available studies^{7,8} reassured that pregnancy did not affect disease-free interval or survival of the patients. The offspring of patients who became pregnant soon after completion of chemotherapy showed no adverse effects from the treatment.

More recent clinical data confirm that women who became pregnant after breast cancer do not have a worse prognosis^{3,4,9-15}.

A meta-analysis by Azim¹⁶ showed that women who got pregnant following breast cancer diagnosis, not only were not negatively affected, but had a 41% reduced risk of death compared to women who did not get pregnant [pooled relative risk

(PRR): 0.59; confidence interval (CI): 0.50-0.70]. The outcome of women with history of breast cancer who became pregnant was compared to breast cancer patients who did not get pregnant and were known to be free of relapse. Even after correcting data for this so called "healthy mother effect", there was no significant difference in survival between groups (PRR: 0.85; 95% CI: 0.53-1.35).

Patients who became pregnant after breast cancer were matched to patients with breast cancer with similar estrogen receptor, nodal status, adjuvant therapy, age and year at diagnosis in a multicenter retrospective cohort study that confirmed this positive effect¹⁷. No difference in disease free survival (DFS) was observed between pregnant and non-pregnant patients in the estrogen receptor positive group [hazard ratio (HR): 0.91; 95% CI: 0.67-1.24] or the estrogen receptor negative cohort (HR: 0.75; 95% CI: 0.51-1.08). The pregnant group had better overall survival (HR: 0.72; 95% CI: 0.54-0.97) with no interaction according to estrogen receptor status.

A recent meta-analysis¹⁸ evaluated the effect of pregnancy on patient survival after surgical treatment for breast cancer. A total of 5 studies were included. Five hundred fifty-four patients who become pregnant after surgical treatment for breast cancer were compared with a control group of 2354 patients for overall survival (OS). The analysis demonstrated that pregnancy after surgical treatment for breast cancer had a significant beneficial effect on OS (PRR, 0.78; 95% confidence interval, 0.64-0.95). The disease-free survival outcome also favored patients in the pregnancy group (PRR, 0.87; 95% confidence interval, 0.71-1.08). This meta-analysis indicates that pregnancy after surgical treatment does not increase the risk of breast cancer recurrence and may actually improve OS.

How to estimate the ovarian reserve after chemotherapy?

Chemotherapy regimens, particularly those including alkylating agents, are notoriously gonadotoxic. They damage ovarian follicles from primary to pre-antral and antral stages, increasing the risk of premature ovarian failure in young women. Ovarian damage can be permanent, leading to premature ovarian failure and/or infertility^{19,20} or temporary, with subsequent recovery of ovarian function. Most of the studies that have addressed the question of reproductive capacity after cancer have focused on predictive markers such as cycle length, pregnancy occurrence and/or basal FSH values. Nevertheless, follicular pool damaging may occur despite recovery of regular menstrual cycles.²¹

Thus more accurate indicators are needed in order to properly inform women about their potential fertility after treatment. Ovarian reserve testing has been introduced in the assisted reproduction setting to predict pregnancy outcome.²² The most studied indicators have been hormonal markers (FSH, E2, inhibin B), and ultrasound tests (Antral follicular count and ovarian volume). These tests have given a realistic evaluation of the reproductive capacity of the ovaries predicting fertility status and the risk of premature ovarian failure.

FSH, E2, and inhibin B reflect ovarian reserve, but fluctuations during menstrual cycle tend to make the determination of ovarian reserve difficult. On the contrary, AMH better reflects the longitudinal decline of oocyte/ follicle remaining stable during menses.²³ Serum anti-Müllerian hormone (AMH) concentrations and ultrasound-determined antral follicle count (AFC) are actually considered the best predictors of ovarian reserve as they strictly correlate both with histological assessment of primordial follicles number, or quantitative response to gonadotrophin stimulation in IVF treatment.

Su et al. dosed AMH, FSH, and inhibin B levels in young women with or without breast cancer. The results showed that AMH, FSH and inhibin B levels did not differ by breast cancer status. For AMH, exploratory analyses suggest that levels may be lower in breast cancer patients older than 37 years of age, compared to healthy controls. These findings support that ovarian reserve, as measured by these biomarkers, is not adversely impacted by the presence of breast cancer in younger women.²⁴ Moreover, measuring these markers could be useful to assess ovarian reserve in patient who underwent chemotherapy and experienced menstrual cycles recovery. For this purpose Anderson & Cameron²¹ recruited 56 premenopausal women with breast cancer. Forty-two women received (neo-) adjuvant chemotherapy. Continuing menses 4–5 yr after diagnosis closely reflected ovarian activity as assessed by a range of serum markers, including estradiol, inhibin B, FSH, and AMH. Pretreatment serum AMH, FSH, antral follicle count, and age predicted late ovarian activity by univariate analysis. However, only AMH was predictive in a multivariate logistic regression

Moreover Su et al²⁵ studied 127 premenopausal breast cancer patients. He reported a significantly lower AMH levels ($P < 0.03$) and a significantly higher ($P < 0.04$) FSH levels in menstruating cancer patients after chemotherapy, compared with age-matched controls.

Yu et al²⁶ measured serum AMH, FSH, and E2 before chemotherapy (baseline) and at weeks 6, 12, 36, and 52 after therapy. They found serum AMH

decreased significantly at 6 weeks and remained suppressed for 52 weeks. E2 levels decreased, and FSH levels increased during chemotherapy; however, at 52 weeks, the levels returned to baseline.

Interestingly, amenorrhoeic and menstruating women were found to have similar AMH values at baseline and at follow-up indicating that rapid reduction in AMH does not appear to be predictive of subsequent menstrual function. Ovarian reserve and endocrine function may be affected differently by chemotherapy.

Anders et al²⁷ analyzed ovarian reserve markers (anti-Müllerian hormone [AMH], follicle-stimulating hormone [FSH], inhibin B) in premenopausal women with early breast cancer before any treatment, in relation to ovarian status at 2 years. They find that pretreatment AMH was significantly lower in women with amenorrhoea at 2 years (4.0 ± 0.9 pmol/L versus 17.2 ± 2.5 , $p < 0.0001$), but FSH and inhibin B did not differ between groups.

Therefore estimating the ovarian reserve through biochemical markers may improve the prediction of ovarian function more than amenorrhoea after chemotherapy.

Which is the right interval between the end of breast cancer treatment and pregnancy?

There are no biological rationale or supporting evidences to define the ideal interval to wait between the end of anticancer treatment and conception.²⁸ Generally it is recommended to avoid pregnancy within 2 years from diagnosis in case of high risk of early relapse.²⁹ In single cases timing could be “personalized” taking into account patient age, risk of relapse, previous treatments and need for adjuvant hormonal therapy.³⁰

The offspring of patients who became pregnant after completion of chemotherapy have shown no adverse effects and congenital anomalies from the treatment^{7,31}, but longer follow up and more studies are necessary before conclusions are drawn. Therefore, the issue of recent cytotoxic treatment remains controversial and further research is required to define a “safety period” between cessation of treatment and pregnancy. In a multicenter retrospective study³² the interval between breast cancer and pregnancy did not seem to impact the risk of relapse.

In breast cancer patients it is still reasonable to postpone pregnancy for 2 years following diagnosis, but the personalized counseling should consider the time of completion of therapy, the risk of relapse, patient’s age and ovarian function and reserve.



Is it safe to stop tamoxifen prematurely in order to achieve a pregnancy?

Conventionally, women requiring tamoxifen for hormone receptor-positive disease were advised to defer pregnancy after at least 5 years of treatment. However, the optimal timing of pregnancy after breast cancer is not clear, and women need to make an informed decision on this issue after discussions with their treating oncologist and fertility specialist taking into consideration their individual preferences and prognosis. The Breast International Group and North American Breast Cancer Group (BIG-NABCG) are going to start a prospective study directed to young women with endocrine sensitive early breast cancer who desire to become pregnant and who are disease free after 18-30 months of adjuvant endocrine therapy. Therapy will be temporarily interrupted to allow conception and patients and offspring outcomes will be investigated, focusing on pregnancy and breast cancer outcomes. Subsequently, endocrine treatment will be resumed, according to patients prognosis and physicians choice. For women with ER-positive disease, continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality, particularly after year 10.³³ What is not clear is if all women need 10 years tamoxifen or other long-term hormonal treatment and if it is safe to temporarily interrupt treatment to achieve pregnancy. For many patients the completion of 5 or 10 years tamoxifen would hinder their chances of future pregnancy, thus the dilemma remains.

Outside clinical trials, it should be made clear that inappropriate endocrine treatment could have potential detrimental effects on breast cancer outcome. Nonetheless, in motivated and informed women, interruption after 2 to 3 years of tamoxifen could be considered, but resumption of tamoxifen following delivery or unsuccessful attempts is strongly advised in these patients.

Is the risk of congenital anomalies increased after breast cancer treatment?

Young cancer patients who plan or experience a pregnancy after cancer diagnosis and treatment ask for the occurrence of congenital abnormalities. According to the literature the risk ranges between 0 and 7.2% closer to the nearly 4% of the general population.^{7, 34, 35}

A Swedish study³⁶ reported the highest incidence of congenital abnormalities in treated breast cancer patients: 7.2%. The tendency towards an increased risk of malformations among the infants was seen especially in the later time period (1988-2002) (OR 2.1,

95% CI 1.2-3.7). Out of 331 first births following breast cancer surgery there were ten cardiac defects (including three children with patent ductus arteriosus and four with septal defects), three kidney/ureterogenesis defects, two undescended testes, two unspecified limb malformations, two ear malformations, two skin malformations, one chromosome anomaly (trisomy 21), one congenital hydrocephaly, and one orofacial cleft. This data come from a selected population where a detection bias is highly plausible.

If chemotherapy is administered during pregnancy, there is a 16% incidence of fetal malformations in the first trimester, but no increased teratogenesis if treatment is started in the second or third trimester.

It has been shown that adjuvant or neoadjuvant chemotherapy with anthracycline (FAC protocol) can be given relatively safely in second and third trimester of pregnancy to treat breast cancer patients^{37,38}.

There are limited data on the use of taxanes or trastuzumab in pregnancy, so if indicated, they should be administered in the postpartum period, as well as radiation or endocrine therapy.³⁹

Is the abortion rate higher?

A relatively higher abortion rate (20-44%) is reported in patients with history of breast cancer as compared to the untreated population.^{40,41}

In a study by Mulvihill et al⁴², it was found that children born to women who conceived after cytotoxic therapy were not at higher risk of congenital anomalies. However, the study reported a 40% rate of premature birth and low birth weight, both of which were attributed to dysfunction of the uterine hormonal gestational milieu. In another study¹³ the high rate of miscarriage (29%) was explained by the older age of the women and changes to ovarian function that can occur after chemotherapy.

A high rate of induced abortions is also described in the literature¹⁵ due to the fear faced by patients and their treating physicians about the safety of pregnancy after breast cancer. This makes pre-conception counseling particularly important: patients must be told that induction of abortion has no impact on maternal prognosis and hence is strongly discouraged for such purposes.⁴³

Are there more obstetric complications in pregnancies after breast cancer?

Cohort studies are reassuring⁴⁴, but the already cited study by Dalberg et al 2006³⁶ reported a higher incidence of birth complications, such as

caesarean section, preterm births, babies with low birth weight, in women previously treated for breast cancer as compared to controls. An increased risk of delivery complications (OR 1.5, 95% CI 1.2-1.9), cesarean section (OR 1.3, 95% CI 1.0-1.7), very preterm birth (<32 wk) (OR 3.2, 95% CI 1.7-6.0), and low birth weight (<1500 g) (OR 2.9, 95% CI 1.4-5.8) were described. Therefore, a close monitoring of pregnancy in women previously treated for cancer is recommended.

Does breast radiotherapy have an effect on pregnancy and lactation?

The effect of radiotherapy analyzed in a study⁴⁵ showed no consequence of radiotherapy on the rate and clinical outcome of pregnancy, and at a mean follow-up of 18 months no anatomical defects were observed in the offspring. In one of the largest studies⁴⁶ of 1624 patients providing information about the influence of radiotherapy on later fertility, there were 23 women who had subsequent pregnancies after a mean time of 30 months (range 6-84 months). Twenty-two of 23 women delivered normal full-term babies, and the remaining patient a low birth-weight infant, with no adverse clinical outcome on pregnancy subsequent to treatment. They reported only diminished lactation from the irradiated breast in those women who had undergone radiotherapy following breast-conserving surgery, which was presumably due to atrophy of the breast lobules. A similar problem with lactation was noticed in a series of 13 patients by Higgins and Hafty⁴⁷, who reported that one patient successfully breastfed following surgery and radiotherapy and three further patients lactated from the treated breast, but were unable to breast feed.

CONCLUSIONS

An increasing number of breast cancer patients will ask their oncologist and gynecologist about fertility and pregnancy after breast cancer.

Recent literature is globally reassuring: pregnancy and lactation after breast cancer are safe. Miscarriages and pregnancy complications seem the same as for general population. There are still some controversies that will be analyzed like the safety of early tamoxifen interruption to allow pregnancy. All patients with newly diagnosed breast cancer patients should receive information about future pregnancy and the other subjects mentioned.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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