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Original article

Pregnancy after breast cancer: Are young patients willing to participate in clinical studies?

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ABSTRACT

Young patients with breast cancer (BC) are often concerned about treatment-induced infertility and express maternity desire. Conception after BC does not seem to affect outcome, but information in estrogen-receptor positive (ER+) disease is not definitive. From September 2012–March 2013, 212 evaluable patients with ER+ early BC, <37 years at diagnosis, from 5 regions (Europe/US/Canada/Middle-East/Australia) answered a survey about fertility concerns, maternity desire and interest in a study of endocrine therapy (ET) interruption to allow pregnancy. Overall, 37% of respondents were interested in the study; younger patients (≤30 years) reported higher interest (57%). Motivation in younger patients treated >30 months was higher (83%) than in older women (14%), interest was independent of age in patients treated for ≤30 months. A prospective study in this patient population seems relevant and feasible. The International-Breast-Cancer-Study-Group (IBCSG), within the Breast-International-Group (BIG) – North-American-Breast-Cancer-Groups (NABCG) collaboration, is launching a study (POSITIVE) addressing ET interruption to allow pregnancy.

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Introduction

Breast cancer (BC) is the most common female malignancy: in the developed world, approximately 7% of patients are diagnosed when <40 years, and BC accounts for more than 40% of all cancers in this age group [1]. A trend of increased incidence in younger Caucasian women has been reported in recent decades [2,3]. In the US, the cumulative risk in 2013 was anticipated to be 1:202 by the age of 40 and 1:26 by the age of 50 [4] with more than 12.000 women <40 years expected to be diagnosed with BC [5].

BC death rates among Caucasian women have consistently decreased since 1990, and this decline is more pronounced in younger women [6]. In a large prospective observational study conducted from 2000 to 2007 and including 2.956 BC patients <40 years at diagnosis, 50% had T1N0 disease: overall, women with estrogen receptor positive (ER+) disease had an 8-year distant disease free and overall survival of 68.3% and 67.5%, respectively [7].

Tamoxifen is the standard adjuvant endocrine therapy (ET) in premenopausal women with ER+ early BC. The substantial reduction (approximately 40%) in both the risk of BC recurrence and BC-related death with 5 years of treatment is independent of age or the use of chemotherapy, with 76% of women alive at 15 years [8]. Recent data from the ATLAS and aTTom studies suggest that continuing tamoxifen to 10 years gives a further significant reduction in recurrence and mortality [9,10]. The recently published results of the Suppression of Ovarian Function Trial (SOFT) showed, after a median follow-up of 67 months, no significant benefit by the addition of ovarian function suppression/ablation (OFS/OA) to tamoxifen in terms of disease-free-survival (DFS) in the overall study population. For women who received adjuvant chemotherapy and remained premenopausal after its completion, the addition of OFS significantly improved disease outcomes, especially if younger <35 years at BC diagnosis [11]. In addition, the results of the joint analysis of the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) in 4.690 patients, showed a significantly improved disease-free survival (DFS) with exemestane plus the GnRH agonist triptorelin, as compared to tamoxifen plus ovarian suppression, with 96% of patients alive at 5 years in both groups [12].

In recent decades, there has been a trend toward delaying childbearing for a variety of reasons (e.g. cultural, educational, professional) so that the median age at first live birth in most developed countries is almost 30 years [13]. As a consequence, BC in young women often occurs before the completion of reproductive plans. Treatment-related infertility significantly impacts quality of life, resulting in substantial distress in young women with BC [14–16]. Fertility concerns influenced treatment decisions in 26% of patients in a large prospective observational study conducted in the US in 620 young women with BC (<40 years) [17]. Significant concern was associated with younger age and no children before BC diagnosis. Of note, only 9% of the respondents reported they did not want a future biologic child because they were afraid this would increase their risk of recurrence. The results of a survey conducted by the European Organization for Research and Treatment of Cancer (EORTC) and BIG in 389 women <35 years at diagnosis of early BC from several countries with different sociocultural attitudes, showed that 59% of participants wanted to have (more) children in the future. Interestingly, among those who did not, almost 40% were afraid of increasing the risk of tumor recurrence [18]. Fear of tumor recurrence might contribute to the low number (<10%) of women with previous BC who subsequently become pregnant [19]. In all reported series this is approximately half the pregnancy rate seen in both age-matched groups without BC and survivors from other cancers [20–22].

The best available retrospective evidence suggests that pregnancy after BC does not increase a woman's risk of disease recurrence [23–27]. In a recent multicenter, retrospective cohort study matching (1:3) patients who became pregnant any time after BC (n = 333) to patients with BC with similar ER and nodal status, adjuvant therapy, age and year of diagnosis (n = 874), after a median follow up of 4.7 years following conception, no difference in 5-year DFS was observed between pregnant and non-pregnant patients in the ER+ population [28]. In the same analysis, no difference in DFS was observed between patients who became pregnant <2 years following BC diagnosis and those who became pregnant afterwards.

Nevertheless, several questions remain unanswered regarding pregnancy in BC survivors, particularly those with ER+ disease. For women desiring children after BC, 5–10 years of ET may substantially reduce the ovarian reserve and the consequent chance of conception; however, a shorter duration of ET in this population has never been prospectively studied. It is therefore crucial to identify strategies allowing some women to become pregnant without waiting for the full standard duration of ET and without compromising their outcome.

Conducting a prospective clinical study of pregnancy after BC is challenging, given the relatively small numbers and the emotional and preference-laden issues involved. Results cannot be achieved without a global commitment by both patients and investigators. In 2009, the IBCSG, within the BIG – NABCG collaboration, committed to an ambitious program aimed to explore the safety of ET interruption in young women with ER+ early BC who wish to have children. A consortium of >50 dedicated investigators from 19 countries across the world was assembled to assess the feasibility of a clinical study in this setting and provide a global perspective of different cultural and social environments. Patients' selection was based on the following assumptions: 1) young BC patients (<40 years at BC diagnosis) face specific issues, including those related to fertility; 2) the rate of follicle loss accelerates around age 35 with an associated reduction in the ability to conceive afterwards; 3) ET for at least 2–3 years has a substantial impact on survival.

Patients' opinion was deemed crucial to successfully plan the development and sustainability of the whole plan. Before launching the project, the consortium decided to test the extent of patients' interest in the research question. A survey to explore young patients' interest in a study addressing pregnancy after BC was therefore launched and conducted worldwide from September 2012 to March 2013.

Patients and methods

Patients' selection included the eligible population for the trial: 1) ER+ early BC; 2) <37 years at BC diagnosis 3) ongoing adjuvant ET [selective estrogen receptor modulator (SERM) alone, LH-RH analog + SERM or aromatase inhibitor (AI)]. Patients could have received adjuvant chemotherapy prior to ET. No additional clinical-pathologic information was collected.

The survey included 8 multiple-choice questions about fertility concerns at BC diagnosis (3 questions), maternity desire (2 questions), current duration of ET (1 question), and willingness to participate in a study of ET interruption to allow pregnancy, if available (2 questions) (Appendix 1). The survey was submitted to patients during routine clinical consultations or by email.

Two-hundred-seventeen consecutive patients from 18 institutions in 5 different regions (Europe/US/Canada/Middle-East/Australia) answered the questionnaire (Table 1, Appendix 2). Most

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Table 1
Accrual by country.

Country	N° of pts surveyed
Australia	67
Italy	46
USA	34
Portugal	14
Switzerland	13
Israel	11
Egypt	10
Saudi Arabia	8
Canada	7
Greece	7
	217

sites surveyed sequential patients during BC clinics, patients from Australia completed the survey on the Breast Cancer Network Australia Website (http://www.bcna.org.au). Five women were excluded (4 were >37 years at diagnosis, 1 did not answer the questions on study participation) for a total of 212 evaluable patients. Age of the 66 patients from Australia was not recorded but all were <37 years: the median age of the remaining 146 patients was 34 years (range 18–37).

The analysis of patients' answers was descriptive, characterizing availability to take part into a clinical trial addressing pregnancy after BC according to geographical region, maternity desire over time, age at BC diagnosis and treatment duration at time of the survey.

Results

Eighty percent of patients (n = 171) discussed the possibility of treatment-related infertility with their doctors at diagnosis and 30% (n = 63) took special steps to preserve fertility. One-hundred-fifteen patients (54%) were somewhat or very concerned about potential infertility, whereas the remaining 97 women (46%) were little or not at all worried.

Patients' answers have been described according to their willingness to participate in the planned clinical study. Overall, 37% of patients were willing to take part in a prospective study, with some regional variation (Table 2). In the subset of patients for whom age at diagnosis was available (n = 146), interest in study participation was observed to be higher (57%) in younger women (≤30 years at diagnosis) (Table 2).

Table 2
Patients interested to participate to the planned clinical study.

	N (%) of patients		N patients
	Interested	Not interested	Responding
Geographic region			
Europe	40 (51)	39 (49)	79
Australia	15 (23)	51 (77)	66
USA/Canada	17 (45)	21 (55)	38
Middle-East	7 (24)	22 (76)	29
Total	79 (37)	133 (63)	212
Age at diagnosis[a]			
≤30 years	13 (57)	10 (33)	23
>30 years	51 (41)	72 (49)	123
Total	64 (44)	82 (56)	146
Duration of ET[b]			
≤30 months	66 (40)	98 (60)	164
>30 months	13 (27)	35 (73)	48
Total	79 (37)	133 (63)	212

[a] Patients for whom age at diagnosis was available (n = 146).
[b] ET: endocrine therapy.

Table 3
Patients interested to participate in the planned clinical study according to treatment duration and age at diagnosis.

Duration of ET[b] and age at diagnosis[a]	N (%) patients		N patients
	Interested	Not interested	Responding
≤30 months of ET[b]			
≤30 years at diagnosis	8 (47)	9 (53)	17
>30 years at diagnosis	49 (45)	60 (55)	109
>30 months of ET[b]			
≤30 years at diagnosis	5 (83)	1 (17)	6
>30 years at diagnosis	2 (14)	12 (86)	14

[a] Patients for whom age at diagnosis was available (n = 146).
[b] ET: endocrine therapy.

Treatment duration

Forty percent of women who received ≤30 months of ET would consider study participation compared with 27% of patients who received >30 months of therapy (Table 2). Age did not influence interest in the study in patients who received ≤30 months of ET. In contrast, in patients who had been on treatment for >30 months, interest in study participation was observed to be higher in younger patients (≤30 years at diagnosis) (83%) compared with women >30 years (14%) (Table 3).

Maternity desire

Maternity desire at the time of survey was compared to what patient's recalled at the time of BC diagnosis (Table 4). The proportion of women who desired children decreased by about a third from BC diagnosis to the time of survey as did their interest in taking part in a study to try to become pregnant, if available, at both time points. This difference did not seem to depend on treatment duration at the time of survey.

Discussion

The best available retrospective evidence suggests pregnancy after BC does not increase the risk of disease recurrence [23–27]; as a consequence, conception should not, in principle, be discouraged, despite a lack of prospective data, particularly in ER+ patients. However, many young women and their care providers face a dilemma: the desire to receive optimal ET versus the desire to have a biologic child. Recent data and clinical experience suggest that some young women do elect to stop ET early to become pregnant [17] despite little to no evidence regarding the potential detrimental effects on their disease outcome. Thus, in order to address this important issue, researchers and clinicians need to prospectively study whether interruption of ET to enable a pregnancy would impact on disease outcomes.

Table 4
Patients interested to participate in the planned clinical study according to maternity desire.

	N (%) patients		N patients
	Interested	Not interested/unsure	Responding
Wish children at present	59 (75)	20 (25)	79
≤30 months of ET[a]	49 (74)	17 (26)	66
>30 months of ET[a]	10 (77)	3 (23)	13
Wish children at diagnosis	74 (94)	5 (6)	79
≤30 months of ET[a]	62 (94)	4 (6)	66
>30 months of ET[a]	12 (92)	1 (8)	13

[a] ET: endocrine therapy.

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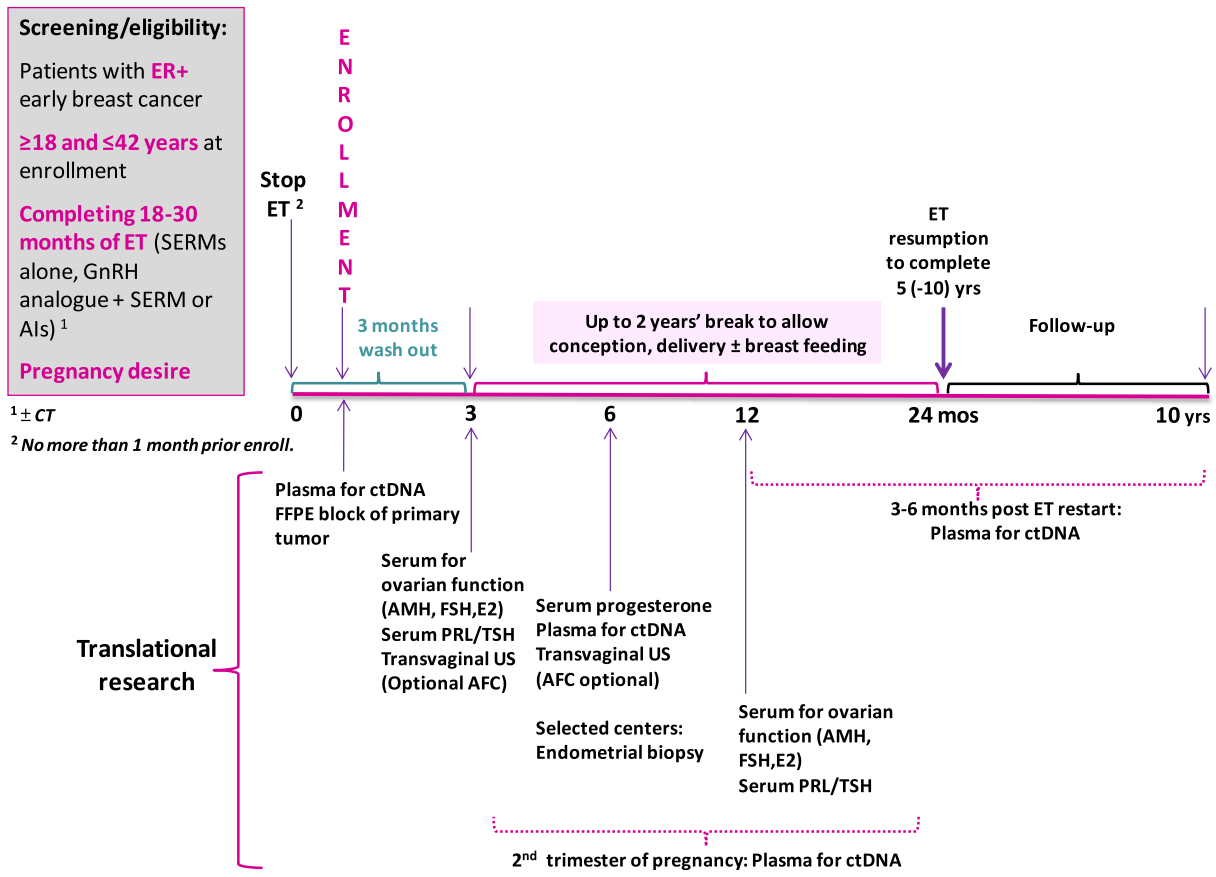

Fig. 1. POSITIVE study design.

The present questionnaire, developed to investigate patients' interest in this research field, showed intriguing results: 1) committed investigators were able to survey a considerable number of patients (217) in just 6 months, thus demonstrating the availability of young patients taking ET for clinical research in this setting; 2) 54% of respondents recalled having been concerned at diagnosis about treatment-related infertility; 3) at the time of the survey, 37% of women were willing to participate in a clinical study, if available.

Factors which seemed to positively influence patients' interest in participating in a clinical study were younger age (≤30 years at diagnosis), shorter treatment duration (≤30 months) and geographical region (Europe/US/Canada). These results may seem somewhat counterintuitive, in particular as young age is generally associated with a higher chance of conceiving after treatment completion. Possible explanations might include patients' need to plan future pregnancy early in their treatment course, regardless of age, and reduced motivation to interrupt ET among patients who are closer to treatment conclusion. The picture could change in the near future as extended adjuvant tamoxifen will expose an increased number of young patients to prolonged treatment and possibly influence their childbearing plans. Based on our data, early treatment interruption could represent an acceptable option for at least 40% of patients, especially if within a clinical study. This underscores the feasibility of a prospective clinical trial testing the safety of interrupting ET in BC patients desiring future conception.

Our survey has a number of limitations; 1) no information on the number of children at BC diagnosis was available in our population. Age at first pregnancy is higher in Western countries and we can therefore assume that a larger proportion of the surveyed patients from these regions were nulliparous at diagnosis, possibly explaining their increased trial interest relative to other geographical regions; 2) the lowest interest in Australian patients could be at least partially explained by online questionnaire compilation which prevented face-to-face discussion with health professionals of the project's aims. On the other hand, breast cancer networks could represent more accurately the average young patients' population; 3) the survey was conducted in selected cancer institutions, over a short period of time, largely in Caucasian patients and results therefore may not be generalizable to the young BC population as a whole; 4) the survey is not exhaustive, for instance did not ask the reason why they would not participate in the clinical study; 5) the questionnaire is not validated.

Current maternity desire (regardless of any possible previous pregnancy) influenced patients' attitudes: the proportion of women who desired children consistently decreased from what recalled at BC diagnosis and impacted trial interest. In our series, the proportion of women who didn't wish for children or were unsure at the time of survey is comparable to that reported both in the large retrospective survey completed on the web by patients belonging to the US Young Survival Coalition [17], and in the EORTC-BIG study in <35 years old European patients with early BC [18]. Both these surveys were submitted to patients whose BC diagnosis was not recent. Overall, these data show that concerns about pregnancy after BC seem to be independent from time since diagnosis, age, geographical, social or cultural differences.

Some important unanswered questions for young women who desire children after BC are: 1) is it safe to interrupt adjuvant ET to conceive?; 2) is it safer to interrupt ET after 30 months or sooner? These questions are relevant both for women who wish to conceive naturally, given the natural decrease in fertility over time, and for women who underwent fertility preservation at the time of diagnosis, who may nonetheless have compelling social and/or psychological reasons to have a baby prior to completing ET.

These questions can only be addressed within a global collaboration: the BIG-NABCG network has recently launched the IBCSG-coordinated trial (**P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine respons**IVE** breast cancer – **POSITIVE** – IBCSG 48-14 – clintrials.gov NCT02308085) (Fig. 1) to assess the risk of BC relapse associated with interrupting ET after having received at least 18 months but no longer than 30 months, to attempt conception. The trial is dedicated to young patients with ER+ early BC who desire children, recognizing that at least for a proportion of these women, 5–10 years of ET may substantially reduce the chance of a successful conception. Interruption of ET, to allow pregnancy, has never been prospectively studied. The primary endpoint of the study is breast cancer free interval (BCFI). Five-hundred patients will be enrolled: the estimated 3-year BCFI failure is 5.6% and 3 interim analyses will permit early trial stopping if the observed incidence of BC recurrences will be higher than anticipated. In addition, the study will collect data on pregnancy (full term pregnancy, caesarean section, abortion, miscarriage, ectopic, stillbirth) and offspring (preterm birth, low birth weight, birth defects) outcomes and patterns of breastfeeding (duration, use of ipsilateral breast if previous breast conservation, side exclusivity). Assisted reproductive technology will be allowed and monitored.

The study will also represent a unique opportunity to describe different parameters related to fertility (menstruation pattern, ovarian reserve, uterine evaluation), the connection of these parameters with the probability of becoming pregnant and add information on breast cancer biology in young women. A psycho-oncology companion study will also explore psychological distress, fertility concerns and decisional conflicts.

The results of the survey support the launch of this global prospective study which is an extraordinary opportunity to test, in a controlled fashion, the different clinical and biological features contributing to the "puzzle" of pregnancy after BC.

Conclusions

This is, to our knowledge, the first prospective analysis on patients' attitudes and interest in a clinical research study to address pregnancy after BC.

The data presented provide additional evidence that maternity desire, especially at diagnosis, is common in young women and should be adequately addressed by healthcare providers. The POSITIVE trial, a global patient-centered prospective study for the care of young women with early BC, will provide healthcare professionals the information they still need to improve personalized treatment and counseling in this population. The information gained will hopefully allow future patients and their care providers to more fully understand the risks and benefits of pregnancy after BC, as well as the true fertility rates in this setting, in particular after interruption of standard ET.

Conflict of interest statement

None declared.

Acknowledgments

We thank the patients who agreed to answer the questionnaire.

Appendix 1

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Patient Survey

1) Before your breast cancer diagnosis, did you wish to have any/any more biologic children in the future?

a) yes
b) no
c) unsure

2) Before starting therapy, did you and your doctors discuss the issue of fertility (ability to become pregnant) after treatment?

a) yes
b) no
c) unsure

3) How many months of endocrine therapy have you received so far?

Months n°: __

4) How concerned were you about the possibility of becoming infertile (unable to become pregnant) after your cancer treatment?

a) not at all concerned
b) a little concerned
c) somewhat concerned
d) very concerned

5) At the present time, do you wish to have any/any more biologic children in the future?

a) yes
b) no
c) unsure

6) Before you began therapy or during therapy, did you take any special steps to lessen the chance that you would become infertile with cancer treatment?

a) yes
b) no
c) unsure

7) Would you be willing to participate in a randomized trial?
Randomization is a method similar to the "flip of a coin" to assign at random (by chance) whether you would stop endocrine treatment now (after 18 months of treatment) or continue it for an additional 18 months before attempting a pregnancy. You will have an equal chance of being placed in one of the two groups:
- Complete 18 months of endocrine treatment _ Attempt pregnancy _ Complete 5 years therapy
- Complete 36 months of endocrine treatment _ Attempt pregnancy _ Complete 5 years therapy

a) yes
b) no

8) If you wouldn't want to participate in this randomized trial, would you agree to complete a survey **focused on fertility and pregnancy, as part of an international registry of young women with breast cancer?**

a) yes
b) no

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Appendix 2

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