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Hormonal factors predictive of fertility in patients with breast cancer interrupting adjuvant endocrine therapy to attempt pregnancy in POSITIVE trial

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ABSTRACT

Purpose: The POSITIVE trial showed that premenopausal women with breast cancer (BC) can safely pause adjuvant endocrine treatment (ET) to attempt conception. 74 % of patients conceived spontaneously or through assisted reproductive technology (ART); Investigating hormonal factors that predict fertility was a key secondary endpoint.
Methods: Hormonal factors were assessed in non-pregnant women at months 3, 6, and 12 after ET interruption. The frequency of low ovarian reserve, defined as anti-Mullerian hormone (AMH) < 0.5 ng/mL at month 3, and of premature ovarian insufficiency (POI), defined as follicle stimulating hormone (FSH) > 25 IU/L at month 12, were primary measures. Secondary analyses to predict pregnancy included AMH, FSH, thyroid stimulating hormone (TSH), prolactin and ovulatory status (defined as progesterone >3 ng/mL at month 6), considering covariates such as age, treatment, and ART use.
Results: Of 518 women enrolled in POSITIVE, 438 were eligible for low ovarian reserve analysis. Low ovarian reserve was observed in 209 women (47.7 %), more frequently among older women and those with prior chemotherapy, but not in relation to ET type or duration. Overall, low ovarian reserve was associated with reduced odds of pregnancy (OR:0.52; 95 % CI:0.31–0.87). Of 142 patients evaluated for POI, 16.7 % of those who received prior chemotherapy experienced POI. FSH at month 3 was associated with POI, but only modestly with spontaneous pregnancy (OR:0.96; 95 %CI: 0.93–1.00); other factors were not predictive of pregnancy.
Conclusion: Hormonal factors are associated with pregnancy in BC patients pausing adjuvant ET to conceive, and their assessment may help to optimize fertility counseling.
Trial registration: ClinicalTrials.gov number NCT02308085.

1. Introduction

Breast cancer (BC) is the most frequent cancer diagnosed in women of reproductive age [1,2]. While prognosis continues to improve, the potential detrimental effects of (neo)adjuvant systemic therapy on fertility may significantly impact treatment decisions, adherence, and future quality of life [3]. Patients with hormone receptor-positive (HR+) BC have traditionally been advised to delay childbearing until completing 5–10 years of adjuvant endocrine therapy (ET), which contributes to reduced fertility due to advancing age [4,5]. Recent findings from the POSITIVE trial, demonstrating no increase in short-term risk of BC recurrence in patients who interrupted ET for pregnancy, will likely lead to an increasing number of patients choosing to temporarily pause treatment to conceive [6]. While most patients became pregnant on POSITIVE, questions remain regarding predictive factors for pregnancy in this population, given the study allowed for natural pregnancy or the use of Assisted Reproductive Technology (ART) [7].

Historically menstruation has served as a surrogate indicator of ovarian function recovery in young BC survivors following treatment [8]. However, even in the presence of continued menstrual cycles, gonadotoxic cancer treatment can lead to a premature depletion of primordial follicles, resulting in a reduced ovarian reserve and, ultimately, premature ovarian insufficiency (POI) - defined as the loss of ovarian function and ability to conceive before the age of 40 [9,10]. The risk of POI makes fertility preservation prior to cancer treatment critically important [10].

The anti-Mullerian Hormone (AMH) level has been recognized as the most accurate marker of ovarian reserve [11]. AMH levels are strong predictors of the number of mature oocytes retrieved during ovarian stimulation cycles [12], however, they do not predict the likelihood of achieving spontaneous pregnancy [13,14]. It has been shown to significantly decrease in BC patients during chemotherapy, with a potential for partial recovery within the first year of follow-up [15–17]. The impact of post-treatment ovarian reserve depletion on the ability to conceive and the risk of POI remain inadequately explored in this population [14]. Further research is needed to evaluate the reliability of post-treatment hormone profile and other potential predictive factors of pregnancy for improving fertility counseling.

Here, we evaluated the hormone profile of the POSITIVE trial cohort to identify hormonal factors after ET interruption predictive of subsequent pregnancy.

2. Patients and methods

2.1. Population

Hormone assessment was a predefined secondary endpoint of the POSITIVE trial, a prospective, international, multicenter, single-arm trial conducted across 20 countries. The study design, patient

[1] Deceased.

characteristics, and primary results were previously described [6,18]. In brief, a total of 518 premenopausal patients aged ≤42 years with stage I to III HR + BC who received adjuvant ET for ≥18 but ≤30 months were enrolled in the trial from December 2014 to December 2019. Patients were recommended to interrupt ET for a maximum of 2 years to attempt pregnancy after a 3-month ET washout period.

The chemotherapy regimens were previously described in the cohort of patients included in the POSITIVE trial. The majority of patients (67.2 %) who received chemotherapy were treated with a combination of anthracycline and taxane therapy. Additionally, 20.6 % received taxane-based therapy while the remaining patients received either anthracycline alone or other chemotherapy regimens [6].

Information on resumption of menstrual cycles and method of conception as well as pregnancy and disease outcomes were previously reported [6,7].

The study was sponsored by the IBCSG in accordance with the International Council for Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local clinical research regulations. All patients gave written informed consent. The IBCSG was responsible for trial design, data collection and management, blood sample centralization, and statistical analysis. Participating centers were affiliated with cooperative groups of the Breast International Group and the United States National Clinical Trials Network.

2.2. Study objectives

This analysis aims to evaluate the risk of low ovarian reserve and POI in POSITIVE trial participants after ET interruption, and to characterize the association of AMH and FSH levels with the likelihood of pregnancy, also considering covariates such as age, adjuvant therapy (ET ± chemotherapy), and use of ART which we previously investigated [7]. Other factors evaluated include thyroid function, prolactin (PRL) and ovulatory status.

2.3. Hormonal assays and definitions

Hormone assessment for patients who were not pregnant included, 3-month post-ET interruption, ovarian reserve (AMH), ovarian function (follicle stimulating hormone -FSH and estradiol -E2), and ovulatory status (progesterone) (Fig. 1). Low ovarian reserve was defined as AMH values < 0.5 ng/ml at month 3 (or at month 12 if AMH at month 3 was not available) [8,15,16]. Ovarian function was evaluated using FSH during the early follicular phase (day 2–5 of the menstrual cycle) at month 3 and at month12 in non-pregnant women. POI was defined as FSH >25IU/L at month 12 during early follicular phase in non-pregnant women [19].If amenorrhea, samples were collected at any time. Ovulatory status was defined as progesterone levels >3 ng/ml in the luteal phase (days 21–25 of the menstrual cycle) at month 6 [20].

FSH, E2, progesterone and AMH were centrally measured as described in the Supplementary Material – Populations and Methods.

Thyroid stimulating hormone (TSH) and PRL levels were assessed locally at month 3 and recorded as 'Normal' or 'High' for PRL, and 'Normal', Low', or 'High' for TSH. If abnormal, PRL and TSH measurements were repeated at month 12.

2.4. Transvaginal Ultrasound

Transvaginal Ultrasound was performed at month 3 to assess, optionally, antral follicular count (AFC).

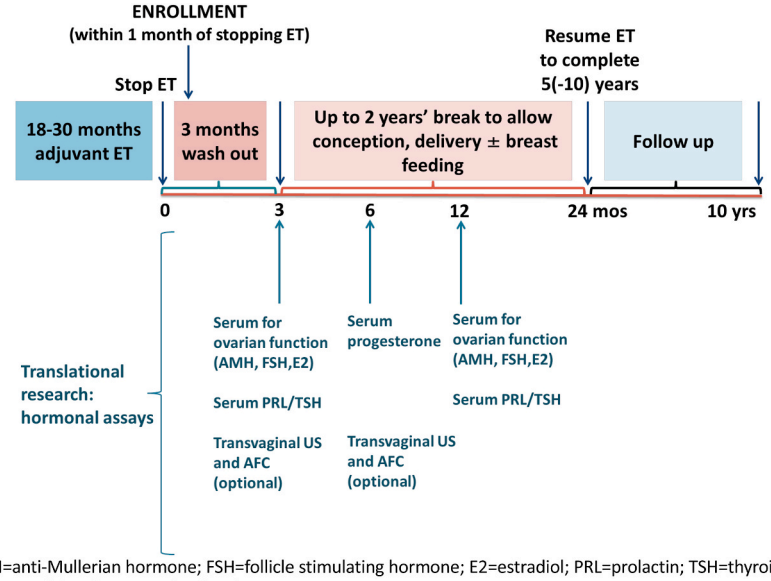
2.5. Statistical methods

The secondary endpoint population consisted of 497 out of the 518 patients enrolled in the POSITIVE trial [6]. Fig. 2 shows the flow diagram of patients in the different analysis populations, further defined in the Supplementary Material – Populations and Methods and Supplementary Table 1.

All AMH samples in non-pregnant women were considered for analysis irrespective of the days of the cycle considering that AMH is stable during the menstrual cycle [21]. Classification of low ovarian reserve (Yes/No) was based on serum AMH samples taken at month 3, or if unavailable, at month 12. Classification of POI (Yes/no) was based on FSH samples taken at months 12. The distribution of FSH and E2 at month 3 post-ET washout was also examined. All FSH and E2 samples taken during pregnancy or outside the menstrual cycle days 2–5 were excluded from analysis, except if the last menstruation occurred >35 days before blood collection as indicative of amenorrhea.

Oligomenorrhea was defined as 120 consecutive days without menstruation and without pregnancy prior to the month 12 sample date.

Categorical data was described as frequency and percent, overall,



AMH=anti-Mullerian hormone; FSH=follicle stimulating hormone; E2=estradiol; PRL=prolactin; TSH=thyroid stimulating hormone; ET= adjuvant endocrine therapy

Fig. 1. Serum collection for hormone assessments and transvaginal ultrasound (US) for endometrium thickness and antral follicular count (AFC) evaluation in the POSITIVE trial.

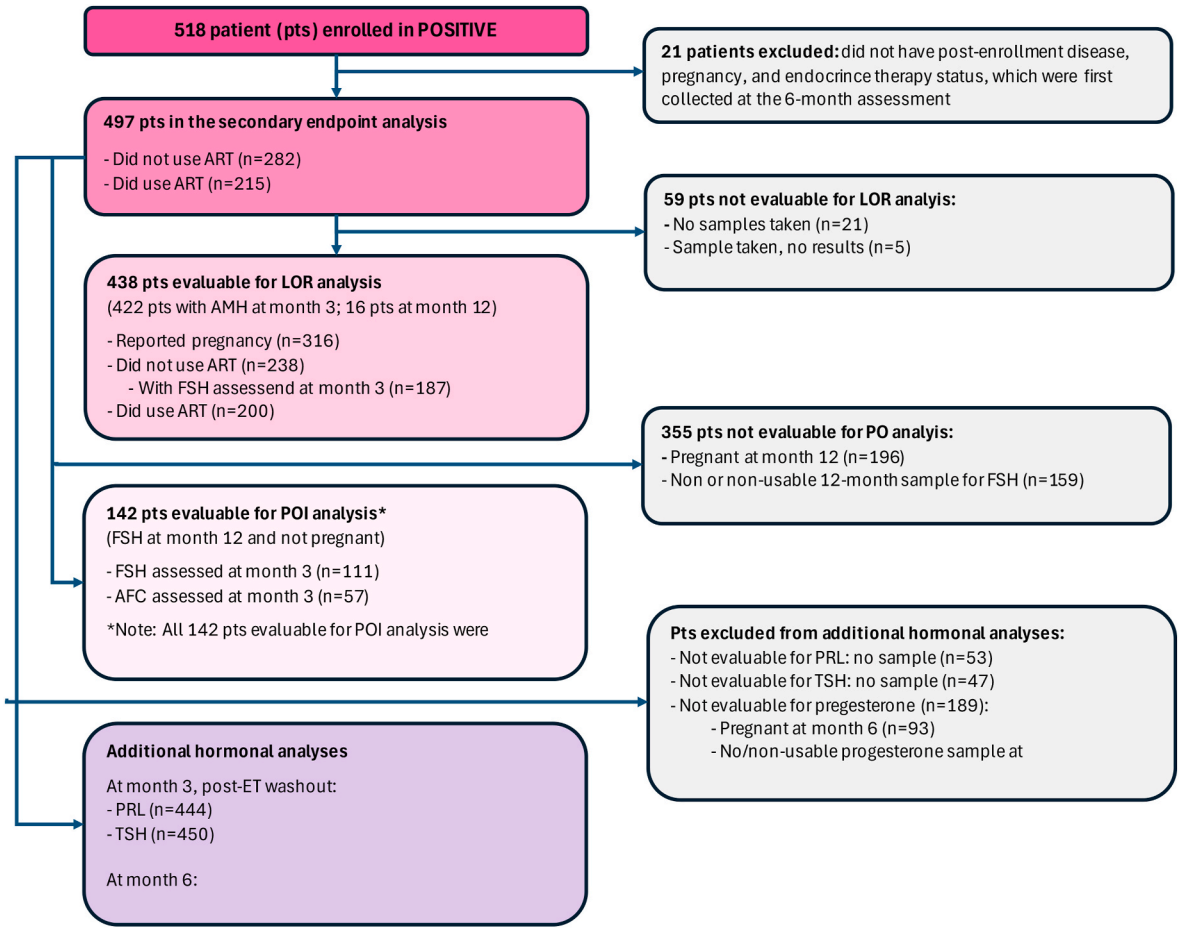


Fig. 2. Flow Chart of the study populations.

and by subgroups as appropriate. Continuous data was summarized as median and interquartile range (IQR) in the manuscript, with full distributions (mean, median, min, max, 25th percentile, and 75th percentile) provided in supplementary tables, overall, and by subgroups as appropriate. Association of factors with binary endpoints such as pregnancy (yes/no) and low ovarian reserve (yes/no) were evaluated using multivariable logistic regression. Multivariable linear regression and correlation estimates were utilized when an outcome was continuous. Details on statistical methods implemented are in the Supplementary Material – Populations and Methods.

3. Results

3.1. Assessment of ovarian reserve

Of 497 women in the secondary analysis population, 438 had useable AMH measurements (Fig. 2), 209 (47.7 %) had low ovarian reserve, defined as AMH <0.5 ng/ml at month 3, or month 12 (Table 1). In a multivariable logistic regression model, younger age (<35 vs. 35–39 or 40–42 years) and no prior chemotherapy (vs. prior chemotherapy) were associated with lower odds of low ovarian reserve (Suppl Table 2). Importantly, neither the type nor the duration of ET were associated with low ovarian reserve.

3.2. Premature ovarian insufficiency (POI)

Of 497 women in the secondary analysis population, 142 patients who were not pregnant at month 12 were eligible for POI analysis, all of whom were also eligible for low ovarian reserve analysis. The median FSH and E2 values at month 12 were 9 IU/L (IQR: 7–14 IU/L) and 44 pg/ml (IQR: 23–77 pg/ml), respectively (Suppl Table 3). Of the 142 patients eligible for POI analysis, 15 (10.6 %) had POI. All 15 women with POI

Table 1
Patient and treatment characteristics according to Low Ovarian Reserve status and according to 12-month Premature Ovarian Insufficiency (POI) status.

	Low ovarian reserve		POI	
	Patients	Number (%) with LOR	Patients	Number (%) with POI
Patients Included in Analysis	438	209 (47.7)	142	15 (10.6)
Age at enrollment (years)				
<35	142	50 (35.2)	40	1 (2.5)
35–39	192	96 (50.0)	58	7 (12.1)
40–42	104	63 (60.6)	44	7 (15.9)
Prior chemotherapy				
No	165	38 (23.0)	52	0 (0.0)
Yes	273	171 (62.6)	90	15 (16.7)
Prior Endocrine Therapy				
OFS±AI	72	34 (47.2)	26	4 (15.4)
SERM only	174	78 (44.8)	47	5 (10.6)
Other	192	97 (50.5)	69	6 (8.7)

OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator.
* Low ovarian reserve is defined as AMH<0.5 ng/ml at month 3, or, if month 3 AMH was not available, AMH<0.5 ng/ml at month 12. Analysis was based on 3-month AMH for 422 non-pregnant patients, and 12-month AMH for 16 non-pregnant patients. POI was defined as FSH level>25 IU/L at month 12.

had received prior chemotherapy (Table 1) and had low ovarian reserve, whereas 46.5 % of those without POI had low ovarian reserve (Suppl Table 4).

As expected, a higher proportion of POI was observed in older patients, with 2.5 % versus 15.9 % POI in patients aged below 35 years and between 40 and 42 years, respectively (Table 1). The duration of ET use was similar between POI and non-POI groups (Suppl Table 5). The proportion of POI was 15.4 % in patients who had prior ovarian function suppression (OFS) with/without aromatase inhibitors (OFS ± AI), 10.6 % of those who received selective estrogen receptor modulator (SERM) only, 8.7 % of those with other ET (Table 1).

The FSH values were available at both months 3 and 12 for 111 of 142 patients. The median 3-month FSH value was 31 IU/L (IQR: 6–45 IU/L) and 7 IU/L (IQR: 6–12 IU/L) in POI (n = 10) and non-POI patients (n = 101) (Suppl Table 6). The Spearman correlation coefficient for FSH values at months 3 and 12 was 0.37 (95 % CI: 0.19–0.52) (Suppl Fig. 1). An univariable logistic regression model showed a modest association between elevated FSH level at month 3 and the occurrence of POI (OR: 1.07; 95 %CI: 1.03 to 1.12).

AFC, an additional marker of ovarian reserve, was available in 57 of the 142 patients eligible for low ovarian reserve and POI analysis. As expected, AFC values were negatively associated with older age and prior chemotherapy. The median AFC was also lower in patients with low ovarian reserve vs patients without low ovarian reserve, and in patients with POI vs without POI (Suppl Table 7).

3.3. AMH and FSH as predictors of pregnancy

A total of 368 (74 %) of the 497 patients in the secondary analysis population reported at least one pregnancy during the study period [7]; while 72 % of patients in the low ovarian reserve analysis population reported at least one pregnancy (316/438). As previously reported [7], younger age and embryo transfer vs. no ART were positively associated with pregnancy, whereas prior chemotherapy and ET type and duration showed no association (Table 2). A multivariable logistic regression model showed that lower AMH values were associated with lower odds of pregnancy (Suppl Table 8). A similar model confirmed that the odds of pregnancy were lower by 48 % for patients with low ovarian reserve (OR: 0.52; 95 % CI: 0.31 to 0.87) (Table 2).

Table 2
Odds ratios for pregnancy (yes vs no) from multivariable logistic model including low ovarian reserve (AMH<0.5 ng/ml), among 438 patients in low ovarian reserve analysis population, of whom 316 became pregnant.

Odds Ratio Estimates			
Factor	Point Estimate	95 % Wald Confidence Limits*	
Low ovarian reserve: Yes vs No	0.523	0.314	0.873
ART: Ovarian stimulation by IVF/ICSI on trial vs No ART	1.096	0.576	2.084
ART: Embryo transfer vs No ART	2.518	1.220	5.195
ART: Other ART vs No ART	1.355	0.716	2.567
Age: <35 vs 40-42	4.641	2.444	8.812
Age: 35–39 vs 40-42	2.708	1.605	4.569
Prior chemotherapy: No vs Yes	0.717	0.423	1.216
Prior ET: SERM only vs OFS±AI	1.066	0.553	2.054
Prior ET: Other vs OFS±AI	1.170	0.608	2.251
Duration prior ET (months)	0.958	0.906	1.013

Note an interaction test (not provided) for the interaction between ART (Yes vs. No) and low ovarian reserve was not statistically significant (p-value: 0.170).
*Factors are considered associated with pregnancy if the 95 % Wald Confidence Limits do not include 1.000.
ART = Assisted Reproductive Technology; IVF/ICSI= In Vitro Fertilization/ Intracytoplasmic Sperm Injection; OFS= Ovarian Function Suppression, AI= Aromatase Inhibitors; SERM= Selective Estrogen Receptor Modulator; ET = Endocrine Therapy.

We observed similar pregnancy rates among women with low ovarian reserve, regardless whether ART was used (Table 3). Although different pregnancy rates were observed for patients with and without low ovarian reserve according to ART use (Table 3), this interaction was not statistically significant (p-value: 0.170). Among 209 patients with low ovarian reserve (AMH <0.5 ng/mL), 49 % utilized ART, compared to 43 % of patients with higher ovarian reserve (AMH ≥1.5 ng/mL); and 43 % of those in between (Suppl Table 9).

Finally, the multivariable logistic regression model, including 187 of 282 patients who did not use ART and had month 3 FSH levels, revealed a very modest association between FSH at month 3 and spontaneous pregnancy (OR: 0.96; 95 %CI 0.93–1.00.) (Suppl Tables 10–11).

3.4. Menstrual cycle characteristics

Among the 127 of 142 patients who did not have POI, 31.5 % (40/127) had experienced oligomenorrhea before month 12 (Suppl Table 12). The distributions of AMH and FSH levels at 3 and 12 months were similar regardless of their oligomenorrhea status during this period (Suppl Table 13).

Of 93 non pregnant patients at month 6 who had useable samples for progesterone and did not use ART, 60.2 % were ovulatory. Multivariable logistic regression showed that ovulatory status at month 6 was not predictive of subsequent spontaneous pregnancy (OR: 1.41; 95 % CI: 0.53–3.74) (Suppl Tables 14–15).

3.5. Prolactin and TSH

Prolactin (PRL) and TSH were evaluated at month 3 post-ET washout in 444 and 450 patients, respectively. Normal values were reported in most patients (Suppl Table 16). Separate multivariable logistic regression models did not show a negative association with pregnancy (Suppl Tables 17–18).

Table 3
Patient and treatment characteristics by use of ART, and pregnancy rates.

	ART[a]		No ART	
	Patients	Number (%) pregnant	Patients	Number (%) pregnant
Ovarian reserve analysis population (n = 438)	200	150 (75.0)	238	166 (69.7)
Low ovarian reserve (AMH<0.5 ng/ml)[a]				
Yes	102	67 (65.7)	107	70 (65.4)
No	98	83 (84.7)	131	96 (73.3)
Age at enrollment (years)				
<35	52	42 (80.8)	90	78 (86.7)
35-39	94	73 (77.7)	98	69 (70.4)
40-42	54	35 (64.8)	50	19 (38.0)
Prior chemotherapy				
No	70	53 (75.7)	95	61 (64.2)
Yes	130	97 (74.6)	143	105 (73.4)
Prior ET				
OFS±AI	33	26 (78.8)	39	26 (66.7)
SERM only	81	57 (70.4)	93	65 (69.9)
Other	86	67 (77.9)	106	75 (70.7)

ART = Assisted Reproductive Technology; IVF/ICSI= In Vitro Fertilization/ Intracytoplasmic Sperm Injection; OFS= Ovarian Function Suppression; AI= Aromatase Inhibitors; SERM= Selective estrogen receptor modulator; ET = Endocrine Therapy.
[a] Although the difference in pregnancy success percentage between low ovarian reserve cohorts (no versus yes) was greater for patients who used ART (19.0 % higher for no low ovarian reserve) than for patients who did not use ART (7.9 % higher for no low ovarian reserve), the interaction test yielded p = 0.170. The covariates in the interaction model for pregnancy were: age, prior chemotherapy, prior ET, duration prior ET, low ovarian reserve (yes/no), and ART (yes/no).

4. Discussion

In this secondary endpoint analysis from the POSITIVE trial that assessed the hormone profiles at 3, 6 and 12 months after interrupting ET, we observed that around half of the eligible cohort experienced low ovarian reserve after the 3-month ET washout. As expected, low ovarian reserve was more frequent in older patients and patients who received prior chemotherapy; however, it was similar across type and duration of ET. Notably, low ovarian reserve was associated with lower odds of pregnancy. Surprisingly, only 10.6 % of patients who were not already pregnant at month 12 experienced POI, despite 63.4 % of them having received chemotherapy. Among those who received chemotherapy, 16.7 % experienced POI. Finally, FSH level at month 3 was associated with POI, but only modestly with pregnancy rates. Other parameters, such as ovulatory status, oligomenorrhea, PRL or TSH were not predictive of spontaneous pregnancy.

This study confirmed that older age and prior chemotherapy are associated with higher likelihood of low ovarian reserve, consistent with other studies [22–24]. The relatively modest incidence of low ovarian reserve in the POSITIVE cohort may be attributed to the young age of the POSITIVE population (cohort's median age was 37 years) [6] and variation in treatments. The impact of the type of chemotherapy regimen was not assessed in this study. Notably, nearly 40 % of patients did not receive chemotherapy, and among these, only 23 % had low ovarian reserve. While previous studies have reported a decrease in AMH levels in women using tamoxifen [22], its impact on fertility remains controversial [25]. Reassuringly, the type and duration of ET, including SERMs, were not associated with hormonal factors or fertility in the POSITIVE cohort.

The low POI rate is consistent with the previous POSITIVE analysis reporting a menstruation recovery rate of nearly 95 % within one year following ET interruption [7]. However, previous studies assessing treatment-related amenorrhea in premenopausal BC survivors showed lower rates of ovarian function recovery after treatment [26–29]. The low POI rate in the POSITIVE trial should be interpreted with caution. Not all patients received chemotherapy, and patients were younger than in most previous studies, being this a trial population who sought pregnancy. Moreover, POI was defined solely based on FSH values, without including oligomenorrhea in the definition [19]. Notably, not all patients with POI experienced oligomenorrhea within the first year, although it may be influenced by the use of ART, introducing a potential bias. Previous studies demonstrated that pregnancy is possible in young cancer survivors with POI, with a spontaneous conception rate of 4–10 % [30–32]. Finally, only patients who were not pregnant at month 12 (those likely facing more fertility issues) were included in the POI analysis. These findings suggest that POI is not the primary reason for not being pregnant at month 12 in the POSITIVE cohort.

We previously showed that 74 % of patients in the POSITIVE trial had at least one pregnancy, most being spontaneous [7]. Although younger age and embryo transfer were the primary factors associated with pregnancy, our current analysis demonstrated that low ovarian reserve was also associated with lower pregnancy rates. While AMH has been traditionally considered a poor predictor of pregnancy, data in cancer survivors remain limited [14]. In patients who receive ART, AMH is associated with lower response to ovarian stimulation and, consequently reduced pregnancy success [33]. However, among 215 patients who performed ART, only 18 underwent ovarian stimulation for IVF. A total of 68 patients underwent cryopreserved embryo transfer, and 17 received embryo/egg donation [7], for which pregnancy success does not depend upon AMH level. In fact, we did not find a significant interaction between ART and low ovarian reserve on pregnancy success. Moreover, the use of ART may be biased by the fact that all patients were actively trying to conceive as soon as possible and may have used their frozen material even when spontaneous conception might have been possible. Overall, these data suggest that attempt at spontaneous conception could also be recommended for patients with low ovarian reserve before ART procedures in this population.

We also assessed FSH level at month 3 as a potential predictor of spontaneous pregnancy. In women with normal menstrual cycle, high FSH levels are considered a marker of sub-fertility in patients using ART, but its predictive value decreases for patients not using ART [34]. Although FSH levels at month 3 were slightly higher in patients who did not achieve pregnancy compared to those who did, median FSH values remained low (<10 IU/L) in both groups. This may explain why FSH at month 3 showed only a modest association with pregnancy outcomes.

While ovulation is necessary for unassisted conception, we did not find a correlation between ovulatory status at month 6 and the likelihood of subsequent spontaneous pregnancy. Ovarian function recovery often occurs within the first year after chemotherapy, but older age is more likely to be associated with lack of or late recovery [35]. Since ovulatory status was determined based on a single luteal progesterone level at month 6, some patients may have resumed ovulatory cycles after our assessment. However, we previously showed that only an additional 4 % of patients resumed menses between months 6 and 12 [7]. This confirms that anovulatory cycles at month 6, as well as oligomenorrhea, did not predict later spontaneous pregnancy in patients who interrupted ET. Likewise, thyroid disease and hyperprolactinemia are both factors associated with ovulatory dysfunction [36] and lower fertility. However, we found that abnormal TSH and PRL values were not associated with lower pregnancy rates. These results should be cautiously interpreted given wide confidence intervals and the small proportion of patients with abnormal TSH and PRL values.

Our findings should be considered in the context of certain limitations. First, time points analyses were limited to 3, 6 and 12 months after ET interruption. Moreover, we included samples collected >35 days without menstruation based on normal menses definition [37]. Patients with longer menstrual cycles may have had an inappropriately timed assessment. The ovulatory cycle may be underestimated in patients with irregular cycles due to reliance on a single progesterone measurement during presumed luteal phase at month 6 in non-pregnant women. This limitation may account for observed low ovulatory cycle rate. Other potential causes of infertility, including male factors, and ovarian reserve before treatment were not reported in the POSITIVE trial. Finally, the secondary endpoints analysis was performed on a relatively small number of eligible patients.

In conclusion, low ovarian reserve was observed in half of the population and was associated with lower pregnancy rates. Nevertheless, around 65 % of patients with low ovarian reserve achieved pregnancy, regardless of the use of ART. As expected, main factors associated with low ovarian reserve were age and chemotherapy, but not the type and duration of ET. Reassuringly, we reported a low incidence of POI in young BC patients who did not achieve pregnancy 12 months after ET interruption. These findings underscore the importance of providing comprehensive fertility counseling to young women who interrupt ET to pursue pregnancy, emphasizing the need for collaboration with reproductive healthcare specialists to optimize conception options. Such counseling ensures both cancer treatment and family planning can be most effectively integrated.

CRediT authorship contribution statement

Isabelle Demeestere: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Samuel M. Niman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **Ann H. Partridge:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Daniela S. Diego:** Writing – review & editing, Writing – original draft. **Roswitha Kammler:** Writing – review & editing, Validation, Supervision, Project administration, Data curation. **Monica Ruggeri:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition, Conceptualization.

Marco Colleoni: Writing – review & editing, Resources. **Chikako Shimizu:** Writing – review & editing, Resources. **Cristina Saura:** Writing – review & editing, Resources. **Karen A. Gelmon:** Writing – review & editing, Resources. **Anna B. Saetersdal:** Writing – review & editing, Resources. **Judith R. Kroep:** Writing – review & editing, Resources. **Audrey Mailliez:** Writing – review & editing, Resources. **Frederic Amant:** Writing – review & editing, Resources. **Manuel Ruız-Borrego:** Writing – review & editing, Resources. **Jeong Eon Lee:** Writing – review & editing, Resources. **Akemi Kataoka:** Writing – review & editing, Resources. **Janice M. Walshe:** Writing – review & editing, Resources. **Junko Takei:** Writing – review & editing, Resources. **Simona Borstnar:** Writing – review & editing, Resources. **Virginia F. Borges:** Writing – review & editing, Resources. **Christobel Saunders:** Writing – review & editing, Resources. **Snezana Susnjar:** Writing – review & editing, Resources. **Vesna Bjelic-Radisic:** Writing – review & editing, Resources. **Fatima Cardoso:** Writing – review & editing, Resources. **Jane Lowe Meisel:** Writing – review & editing, Resources. **Jennifer F. Kawwass:** Writing – review & editing. **Tanja Spanic:** Writing – review & editing, Resources. **Sarra El-Abed:** Writing – review & editing, Resources. **Martine Piccart:** Writing – review & editing, Funding acquisition. **Larissa A. Korde:** Writing – review & editing, Conceptualization. **Aron Goldhirsch:** Writing – review & editing, Conceptualization. **Richard D. Gelber:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Olivia Pagani:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Hatem A. Azim:** Writing – review & editing, Supervision, Conceptualization. **Fedro A. Peccatori:** Writing – review & editing, Supervision, Resources, Conceptualization.

Prior presentation

An abstract of this work has been accepted for oral presentation at the 2025 ESMO Breast Cancer Annual Congress.

Ethical approval statement

The study was sponsored by the IBCSG in accordance with the International Council for Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local clinical research regulations. The protocol was approved by the institutional review board at each participating center. All patients gave written informed consent.

Data sharing statement

After publication, access to de-identified participant data may be requested by researchers by submitting a proposal (to stat_center@ibcsg.org), which will be reviewed for scientific merit and feasibility in accordance with IBCSG guidelines for collaborative research and data sharing policy (https://www.ibcsg.org/en/patients-professionals/research-collaboration).

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Declaration of competing interest

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Appendix A. Supplementary data

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