Fertility Preservation and Assisted Reproduction in Patients With Breast Cancer Interrupting Adjuvant Endocrine Therapy to Attempt Pregnancy

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ABSTRACT

PURPOSE We investigated time to pregnancy, efficacy and safety of fertility preservation, and assisted reproductive technologies (ARTs) in women with early hormone receptor–positive breast cancer (BC) desiring future pregnancy.

PATIENTS AND METHODS POSITIVE is an international, single-arm, prospective trial, in which 518 women temporarily interrupted adjuvant endocrine therapy to attempt pregnancy. We evaluated menstruation recovery and factors associated with time to pregnancy and investigated if ART use was associated with achieving pregnancy. The cumulative incidence of BC-free interval (BCFI) events was estimated according to the use of ovarian stimulation at diagnosis. The median follow-up was 41 months.

RESULTS Two hundred seventy-three patients (53%) reported amenorrhea at enrollment, of whom 94% resumed menses within 12 months. Among 497 patients evaluable for pregnancy, 368 (74%) reported at least one pregnancy. Young age was the main factor associated with shorter time to pregnancy with cumulative incidences of pregnancy by 1 year of 63.5%, 54.3%, and 37.7% for patients age <35, 35-39, and 40-42 years, respectively. One hundred and seventy-nine patients (36%) had embryo/oocyte cryopreservation at diagnosis, of whom 68 reported embryo transfer after enrollment. Cryopreserved embryo transfer was the only ART associated with higher chance of pregnancy (odds ratio, 2.41 [95% CI, 1.75 to 4.95]). The cumulative incidence of BCFI events at 3 years was similar for women who underwent ovarian stimulation for cryopreservation at diagnosis, 9.7% (95% CI, 6.0 to 15.4), compared with those who did not, 8.7% (95% CI, 6.0 to 12.5).

CONCLUSION In POSITIVE, fertility preservation using ovarian stimulation was not associated with short-term detrimental impact on cancer prognosis. Pregnancy rates were highest among those who underwent embryo/oocyte cryopreservation followed by embryo transfer.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Retrospective data have demonstrated the safety of pregnancy after breast cancer (BC), even in patients with hormone receptor–positive disease.[1-3] Yet, the optimal duration of adjuvant endocrine therapy (ET) of 5-10 years, during which pregnancy is contraindicated, substantially challenges the feasibility of future pregnancies given the decline of fertility potential over time.[4] Recently, the primary results of the POSITIVE trial demonstrated that temporary interruption of ET to attempt pregnancy does not increase the short-term risk of disease recurrence.[5] However, other challenges still exist regarding the likelihood of becoming pregnant. These include the detrimental impact of chemotherapy on ovarian reserve[6] and the uncertainty regarding safety and efficacy of assisted reproductive technologies (ARTs) in this population.

CONTEXT

Key Objectives

The POSITIVE trial demonstrated that temporary interruption of endocrine therapy (ET) in women with hormone receptor–positive breast cancer (BC) to attempt pregnancy does not increase the short-term risk of recurrence. This secondary analysis evaluated the association between the use of ovarian stimulation for fertility preservation, or assisted reproductive technologies (ARTs), and BC outcome. Other objectives included time to menstruation recovery and time to pregnancy in addition to the association between the use of ART and chance of pregnancy.

Knowledge Generated

Embryo/oocyte cryopreservation at BC diagnosis followed by embryo transfer after ET interruption had higher pregnancy rates and was not associated with worse prognosis. Menstruation resumptions occurred mostly during the first 6 months, with young age being the most determinant factor.

Relevance *(G. Fleming)*

These data provide further rationale for oncologists to encourage their young patients with hormone-receptor-positive BC who desire future childbearing to see a fertility specialist for embryo/oocyte cryopreservation prior to initiation of systemic therapy.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

Nevertheless, given the importance of future fertility for young survivors,[7,8] all major guidelines highlight the importance of fertility counseling before initiation of primary therapy in young patients with BC.[9-12] Embryo cryopreservation and oocyte cryopreservation are considered as reliable tools to preserve fertility in these women. Yet, concerns remain regarding the potential detrimental effect of the use of ovarian stimulation required for embryo or oocyte cryopreservation, particularly in the setting of a hormone receptor–positive cancer. In addition, prospective data are lacking on the efficacy and safety of ovarian stimulation and other ART strategies in young BC survivors.

Here, we report on fertility preservation and ART use in the POSITIVE trial, which, to our knowledge, is the only prospective study to date to evaluate oncologic and reproductive outcomes of women attempting pregnancy after BC.[5]

PATIENTS AND METHODS

Study Design

POSITIVE is a prospective, international, multicenter, investigator-initiated, single-arm trial that enrolled 518 patients across 20 countries from December 2014 to December 2019. Detailed information regarding patient characteristics and primary end point analysis was previously published.[5,13] Briefly, eligible women had stage I to III hormone receptor–positive BC, were 42 years and younger at enrollment, and received 18-30 months of adjuvant ET before inclusion. All patients underwent a 3-month washout period after cessation of ET before attempting pregnancy. Per protocol, the duration of interruption of ET could be up to 2 years.

Information regarding the use of fertility preservation at diagnosis was collected at study entry. Fertility preservation methods included the use of gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy, ovarian stimulation followed by embryo and/or oocyte cryopreservation, or ovarian tissue cryopreservation.

After enrollment, all patients were asked to complete a menstruation diary to prospectively collect menstrual cycle dates through the first 2 years on study. As per protocol, the use of any ART modality on study was allowed at the investigator and patient discretion. It included transfer of cryopreserved embryo(s) in patients who underwent embryo/oocyte cryopreservation before enrollment, ovarian stimulation for in vitro fertilization (IVF), intrauterine insemination, clomiphene use, embryo/egg donation, and ovarian tissue transplantation. Data on the use of ART were collected for 2 years after study entry, corresponding to the maximum expected duration of temporary interruption of ET.

The POSITIVE trial was sponsored by the International Breast Cancer Study Group (IBCSG), which is responsible for data management and statistical analysis. The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and local clinical research regulations. All patients provided written informed consent.

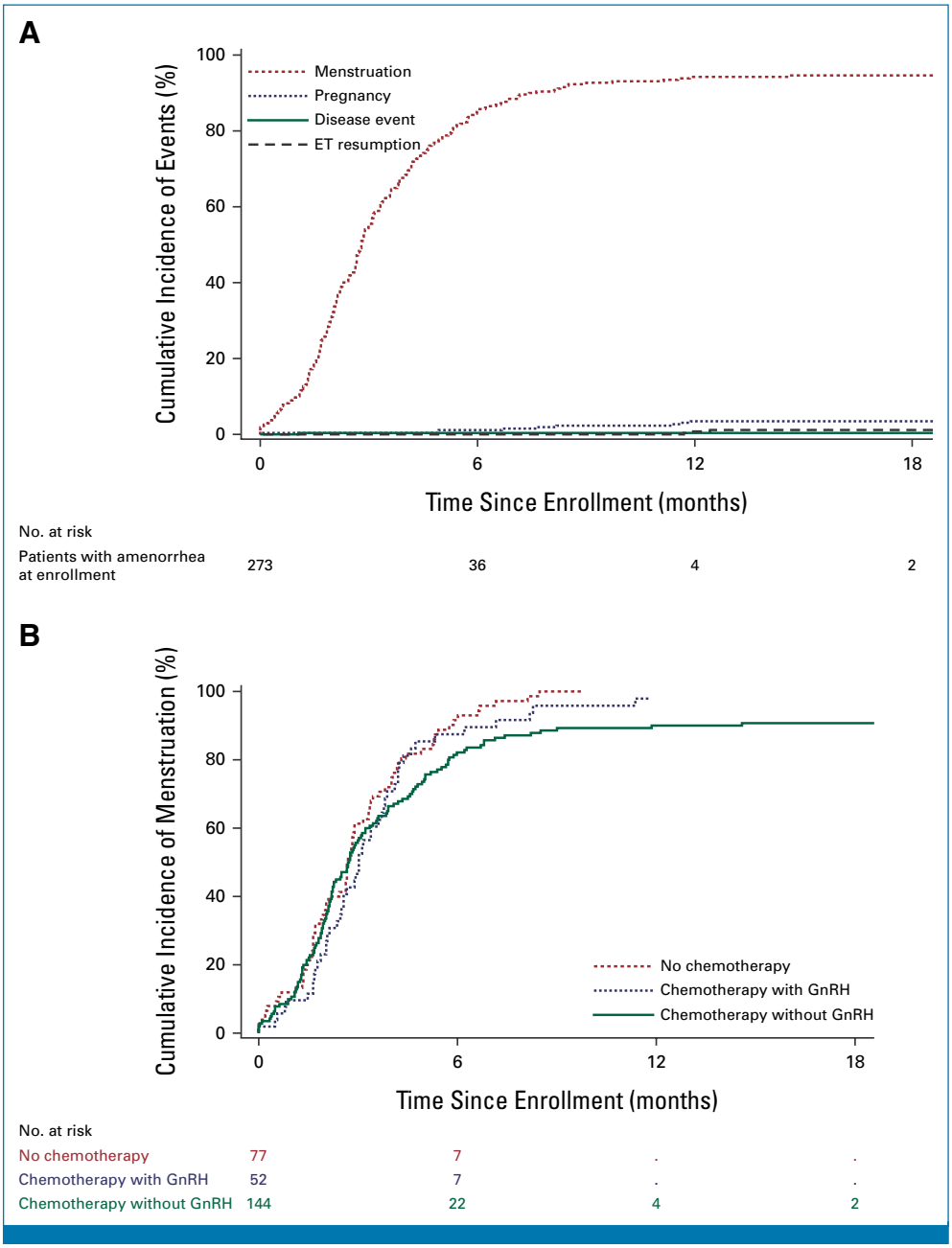

FIG 1. Cumulative incidence of menstruation recovery, in the presence of competing risks (competing events that occur before menstruation recovery), among 273 women in the POSITIVE trial who had persistent amenorrhea at enrollment. (A) Recovery in all patients (also showing curves for competing events occurring before menstruation recovery). (B) Recovery according to no previous chemotherapy use and the previous use of chemotherapy with or without GnRH analogs for fertility preservation (curves for competing events occurring before menstruation recovery are not shown). GnRH, gonadotropin-releasing hormone.

Study Objectives

Menstruation resumption and use of ART were predefined secondary end points of the POSITIVE trial. The main objective of the analysis is to evaluate the association between the use of ovarian stimulation for fertility preservation, or as a part of ART, and BC outcome. Other objectives included the evaluation of factors associated with time to menstruation recovery and time to pregnancy after ET interruption in addition to investigating the chance of pregnancy associated with the use of ART.

Statistical Analysis

Of the 518 enrolled patients, 516 were evaluable for the primary efficacy analysis and 497 had sufficient information

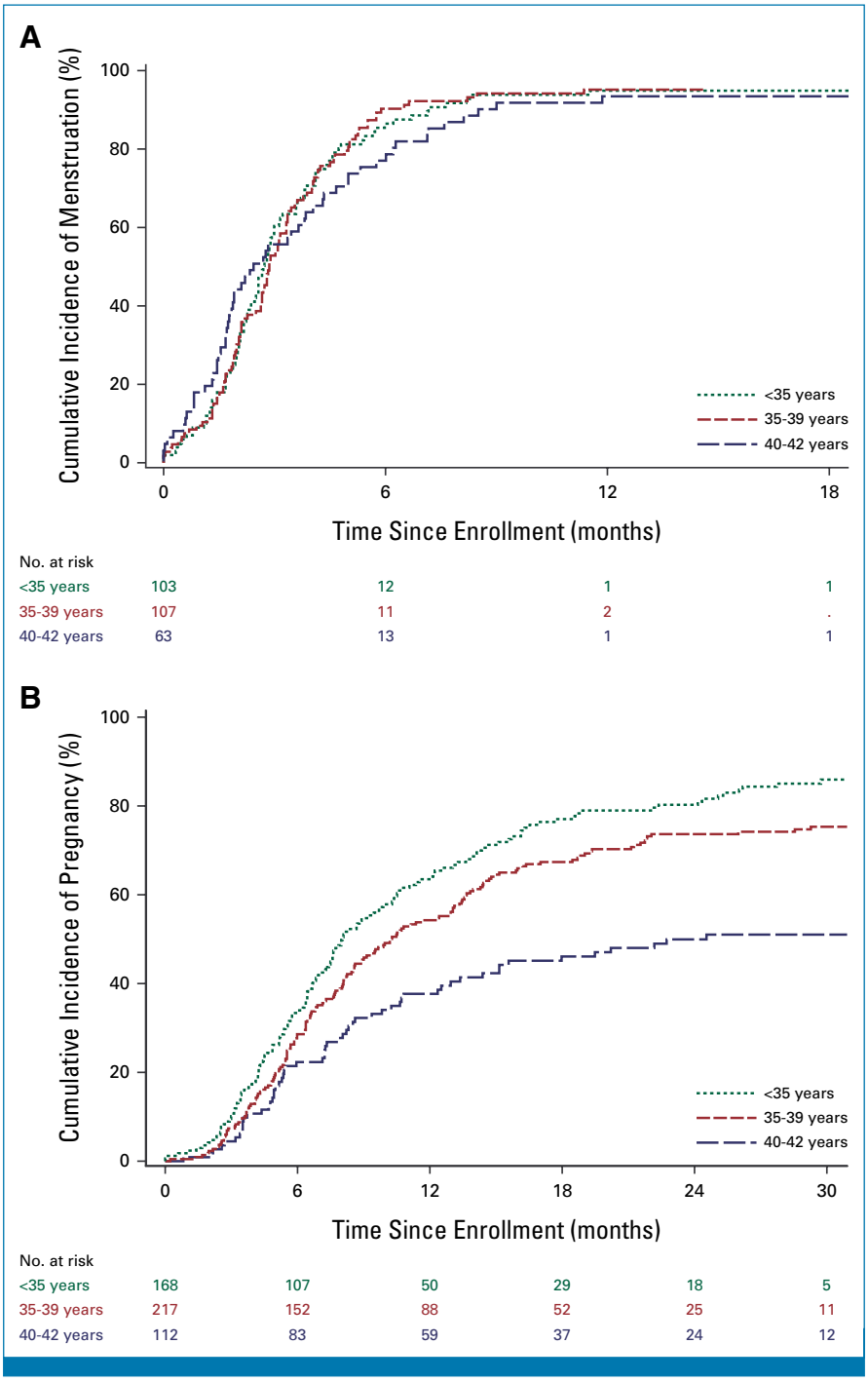

FIG 2. (A) Cumulative incidence of menstruation recovery over time by age among the 273 patients who had amenorrhea at enrollment, in the presence of competing risks. At 6 and 12 months from enrollment, patients younger than 35 years had a cumulative incidence of menstruation recovery of 85.4% (95% CI, 76.4 to 91.2) and 93.8% (95% CI, 86.1 to 97.3), respectively, compared with 89.3% (95% CI, 81.3 to 94.0) and 95.1% (95% CI, 88.2 to 98.1) in patients age 35-39 years and 75.4% (95% CI, 62.2 to 84.5) and 93.4% (95% CI, 81.6 to 97.8), in patients age 40-42 years. (B) Cumulative incidence of pregnancy over time since enrollment, in the presence of competing risks, among 497 women in the POSITIVE trial according to age at enrollment. At 1 and 2 years from enrollment, patients younger than 35 years had a cumulative incidence of pregnancy of 63.5% (95% CI, 55.6 to 70.4) and 80.3% (95% CI, 73.1 to 85.7), respectively, compared with 54.3% (95% CI, 47.4 to 60.7) and 73.7% (95% CI, 67.1 to 79.1) in patients age 35-39 years and 37.7% (95% CI, 28.7 to 46.6) and 50% (95% CI, 40.2 to 59.0) in patients age 40-42 years.

to assess pregnancy outcomes, ART, and fertility preservation[5] (Appendix Fig A1, online only). Menstruation recovery analysis included 273 patients from the primary efficacy analysis population who had persistent amenorrhea at enrollment.

A patient was considered to have recovered menstruation if at least one menstruation date was documented after enrollment. Menstruation-free interval was defined as the months from enrollment to menstruation recovery or the occurrence of any competing risk, including ET resumption, pregnancy, or cancer event, whichever occurred first. Patients not experiencing menstruation recovery or a competing event were censored at the last date menstruation status would have been collected. The cumulative incidence of menstruation recovery in the presence of competing risks was estimated at six and 12 months. To determine factors associated with time to first menstruation, a multivariable Fine and Gray[14] competing risk model was used including the following covariates: age at enrollment, HER2 status, previous chemotherapy with concurrent GnRHa for fertility preservation, menstruation before diagnosis, and previous ET. The cumulative incidence of menstruation recovery in the presence of competing risks was also estimated according to the previous use of chemotherapy with or without GnRHa.

Pregnancy-free interval was defined as the months from enrollment to the date of first event, either pregnancy or any competing risk, including: ET resumption, cancer event, or date patient indicated they were no longer trying to become pregnant. Patients not experiencing an event were censored at the date of last follow-up. The cumulative incidence of first pregnancy was estimated at 1 and 2 years. Multivariable Fine and Gray competing risk models were used to evaluate pregnancy-free interval in relation to age, previous chemotherapy with or without GnRHa use for fertility preservation, previous parity, type of ET, and menstruation status at enrollment.

A multivariable logistic regression model was used to estimate the odds ratios (ORs) of achieving pregnancy. The model featured the covariates of age, ART use, and use of previous chemotherapy with or without GnRHa.

Breast cancer–free interval (BCFI) was defined as the time from enrollment to the first invasive BC event (local, regional, or distant recurrence or a new invasive contralateral BC). In the absence of an event, BCFI was censored at the date the patient was last known to be BC-free.

The cumulative incidence (1-Kaplan-Meier) of BCFI events at 3 years was estimated according to ovarian stimulation reported at diagnosis. Landmark analysis at 24 months was used to estimate the cumulative incidence of BCFI events by ovarian stimulation as a part of ART after enrollment. Median follow-up was estimated using the reverse Kaplan-Meier method.

RESULTS

Menstruation Recovery

All 516 patients included in the primary analysis of POSITIVE stopped ET within 1 month of study entry. Two hundred seventy-three patients (53%) reported amenorrhea at the time of enrollment, of whom 232 patients (85%) were treated with GnRHa as part of adjuvant ET.

At 12 months, 94.2% (95% CI, 90.5 to 96.5) of amenorrheic patients resumed menses with only one patient recovering menses >12 months (Fig 1A). Only 18 patients did not report menstruation recovery after enrollment, of whom four had no postbaseline follow-up. Patients who did not resume menses had a slightly higher median number of chemotherapy cycles (7.5 *v* 6.0), older median age (38.5 *v* 36.0 years), and longer median time from diagnosis to suspension of ET (32.0 *v* 28.7 months).

Among the 273 patients who had amenorrhea at enrollment, the cumulative incidence of menstruation recovery at 6 months was 90.2% (95% CI, 80.1 to 95.3) for those who had not received chemotherapy, compared with 85.4% (95% CI, 71.2 to 92.9) and 81.4% (95% CI, 73.8 to 87.0) for women who had received chemotherapy with or without GnRHa, respectively (Fig 1B). In a multivariable model, no factor was significantly associated with time to menstruation recovery, including age (Appendix Table A1, Fig 2A).

Time to Pregnancy

Four hundred ninety-seven patients were evaluable for pregnancy outcomes. At a median follow-up of 41 months, 74% of patients (n = 368) had at least one pregnancy.

At 1 and 2 years from enrollment, the cumulative incidence of pregnancy was 53.6% (95% CI, 49.1 to 57.9) and 70.5% (95% CI, 66.2 to 74.4), respectively. A clear association was observed between young age and higher cumulative incidence of pregnancy at both time points (Fig 2).

In a multivariable Fine and Gray competing risks model, only younger age was associated with shorter time to pregnancy; subdistribution hazard ratio (sHR): 0.74 (95% CI, 0.59 to 0.93) and 0.40 (95% CI, 0.29 to 0.56) for patients age 35-39 and 40-42 years, respectively, in comparison with patients younger than 35 years. Neither GnRHa use during chemotherapy nor the type of ET were associated with time to pregnancy (Appendix Table A2).

Fertility Preservation and ART Procedures

Two hundred fifty-two of the 497 patients (51%) underwent some form of fertility preservation procedure soon after their BC diagnosis. This included 179 patients (36%) who had ovarian stimulation for embryo/oocyte cryopreservation, 67

TABLE 1. Patient Characteristics of Main Fertility Preservation and Assisted Reproductive Technologies Subgroups

	All Secondary End Point Population Patients	Embryo/Oocyte Cryopreservation Before Enrollment	Cryopreserved Embryo Transfer After Enrollment	Ovarian Stimulation for IVF After Enrollment
Characteristic	No. (%)	No. (%)	No. (%)	No. (%)
Total	497 (100)	179 (100)	68 (100)	80 (100)
Age at enrollment (years)				
<35	168 (33.8)	55 (30.7)	16 (23.5)	23 (28.8)
35-39	217 (43.7)	82 (45.8)	32 (47.1)	40 (50.0)
40-42	112 (22.5)	42 (23.5)	20 (29.4)	17 (21.3)
Tumor size				
≤2 cm	319 (64.2)	110 (61.5)	42 (61.8)	51 (63.8)
>2 cm	176 (35.4)	68 (38.0)	26 (38.2)	29 (36.3)
Unknown	2 (0.4)	1 (0.6)		
LN+				
pN0	327 (65.8)	112 (62.5)	38 (55.9)	56 (70.0)
pN+	170 (34.2)	67 (37.4)	30 (44.1)	24 (30.0)
Previous neo/adjuvant chemo				
No	189 (38.0)	52 (29.1)	20 (29.4)	30 (37.5)
Yes	308 (62.0)	127 (70.9)	48 (70.6)	50 (62.5)
Previous endocrine therapy				
SERM only	206 (41.4)	72 (40.2)	25 (36.8)	25 (31.3)
SERM + OFS	177 (35.6)	66 (36.9)	24 (35.3)	35 (43.8)
AI + OFS	79 (15.9)	29 (16.2)	14 (20.6)	13 (16.3)
Other[a]	35 (7.0)	12 (6.7)	5 (7.4)	7 (8.8)
Previous live birth				
No	374 (75.3)	152 (84.9)	57 (83.8)	70 (87.5)
Yes	123 (24.7)	27 (15.1)	11 (16.2)	10 (12.5)

Abbreviations: AI, aromatase inhibitor; IVF, in vitro fertilization; LN+, lymph node positive; OFS, ovarian function suppression; SERM, selective estrogen receptor modulator.
[a]Other included 32 patients who had SERM + AI + OFS, two patients who had SERM + AI, and one patient who had OFS only.

TABLE 2. Pregnancy Rates According to the Use of Fertility Preservation Methods and ART

	On-Trial Pregnancy	
	Yes	No
Patient Group	No. (%)	No. (%)
All secondary end point population patients	368 (74.0)	129 (26.0)
Age at enrollment (years)		
<35	144 (85.7)	24 (14.3)
35-39	165 (76.0)	52 (24.0)
40-42	59 (52.7)	53 (47.3)
Previous chemotherapy with concurrent GnRHa for fertility preservation		
Chemotherapy with GnRHa	53 (79.1)	14 (20.9)
Chemotherapy without GnRHa	180 (74.7)	61 (25.3)
No chemotherapy	135 (71.4)	54 (28.6)
Embryo/oocyte cryopreservation before enrollment		
Yes	143 (79.9)	36 (20.1)
No	225 (70.8)	93 (29.2)
ART use after enrollment		
Ovarian stimulation for IVF	54 (67.5)	26 (32.5)
Cryopreserved embryo transfer	56 (82.4)	12 (17.6)
Other ART	53 (79.1)	14 (20.9)
No ART	205 (72.7)	77 (27.3)

Abbreviations: ART, assisted reproductive technology; GnRHa, gonadotropin-releasing hormone analogs; IVF, in vitro fertilization; LN+, lymph node–positive.

(13%) who received GnRHa during chemotherapy, and 30 (6%) who had ovarian tissue cryopreservation. Among the 179 patients who had undergone ovarian stimulation for embryo/oocyte cryopreservation at diagnosis, 83 (46%), 36 (20%), and 65 (37%) patients reported using gonadotropins alone, gonadotropins with tamoxifen, or gonadotropins with letrozole for ovarian stimulation, respectively. Five patients used more than one stimulation protocol.

Patients who underwent embryo/oocyte cryopreservation at diagnosis were more likely to be nulliparous (85% *v* 70%), were treated with chemotherapy (71% *v* 57%), and have node-positive disease (37% *v* 32%). Sixty-eight of 179 patients (38%) reported cryopreserved embryo transfer after enrollment.

ART procedures were performed after enrollment in 215 patients (43%). Some patients might have undergone more than one procedure. Eighty patients (16%) underwent ovarian stimulation for IVF, 68 patients (14%) underwent cryopreserved embryo transfer, 37 (7%) underwent intrauterine insemination, 19 (4%) received clomiphene, 17 (3%) received embryo/egg donation, and two patients (<1%) received ovarian transplantation.

Table 1 summarizes patient characteristics according to main fertility preservation and ART modalities.

ART Use and Chance of Pregnancy

Table 2 summarizes pregnancy rates according to the use of ART and fertility preservation methods.

We performed a multivariable logistic regression model to evaluate the association between ART use and achieving pregnancy (Table 3). Cryopreserved embryo transfer was the only modality associated with a higher chance of pregnancy (OR, 2.41 [95% CI, 1.17 to 4.95]). Age was a strong predictor of becoming pregnant; OR, 0.50 (95% CI, 0.29 to 0.86) and OR, 0.16 (95% CI, 0.08 to 0.29) for patients age 35-39 and 40-42 years, respectively, compared with those younger than 35 years.

Ovarian Stimulation and Breast Cancer Outcome

As a Part of Embryo/Oocyte Cryopreservation—At Diagnosis

At 3 years, the cumulative incidence of BCFI events was 9.7% (95% CI, 6.0 to 15.4) for the 179 patients who underwent ovarian stimulation for embryo/oocyte cryopreservation at diagnosis and 8.7% (95% CI, 6.0 to 12.5) for the 318 patients who did not (Fig 3A).

As a Part of ART—After Enrollment

A 24-month landmark analysis of patients who were breast cancer–free and in follow-up was used to compare BCFI among those who underwent ovarian stimulation for IVF (71 of 80 reached the 24-month landmark) with those who did not (326 of 436 reached the landmark; Fig 3B). Only two and eight patients, respectively, had a BCFI event within the follow-up of 18 months from the landmark.

TABLE 3. Multivariable Model Evaluating the Association of ART Methods on Achieving Pregnancy

Comparison	OR (95% confidence interval)
35-39 years *v* < 35 years	0.50 (0.29 to 0.86)
40-42 years *v* < 35 years	0.16 (0.08 to 0.29)
Ovarian stimulation for IVF after enrollment *v* no ART	0.85 (0.48 to 1.50)
Cryopreserved embryo transfer *v* no ART	2.41 (1.17 to 4.95)
Other ART *v* no ART	1.81 (0.92 to 3.57)
Chemotherapy with GnRHa *v* chemotherapy no GnRHa[a]	1.41 (0.70 to 2.82)
No chemotherapy *v* chemotherapy no GnRHa	1.10 (0.70 to 1.75)

Abbreviations: ART, assisted reproductive technology; GnRHa, gonadotropin-releasing hormone analogs; IVF, in vitro fertilization; OR, odds ratio.

[a]Chemotherapy and GnRHa for fertility preservation.

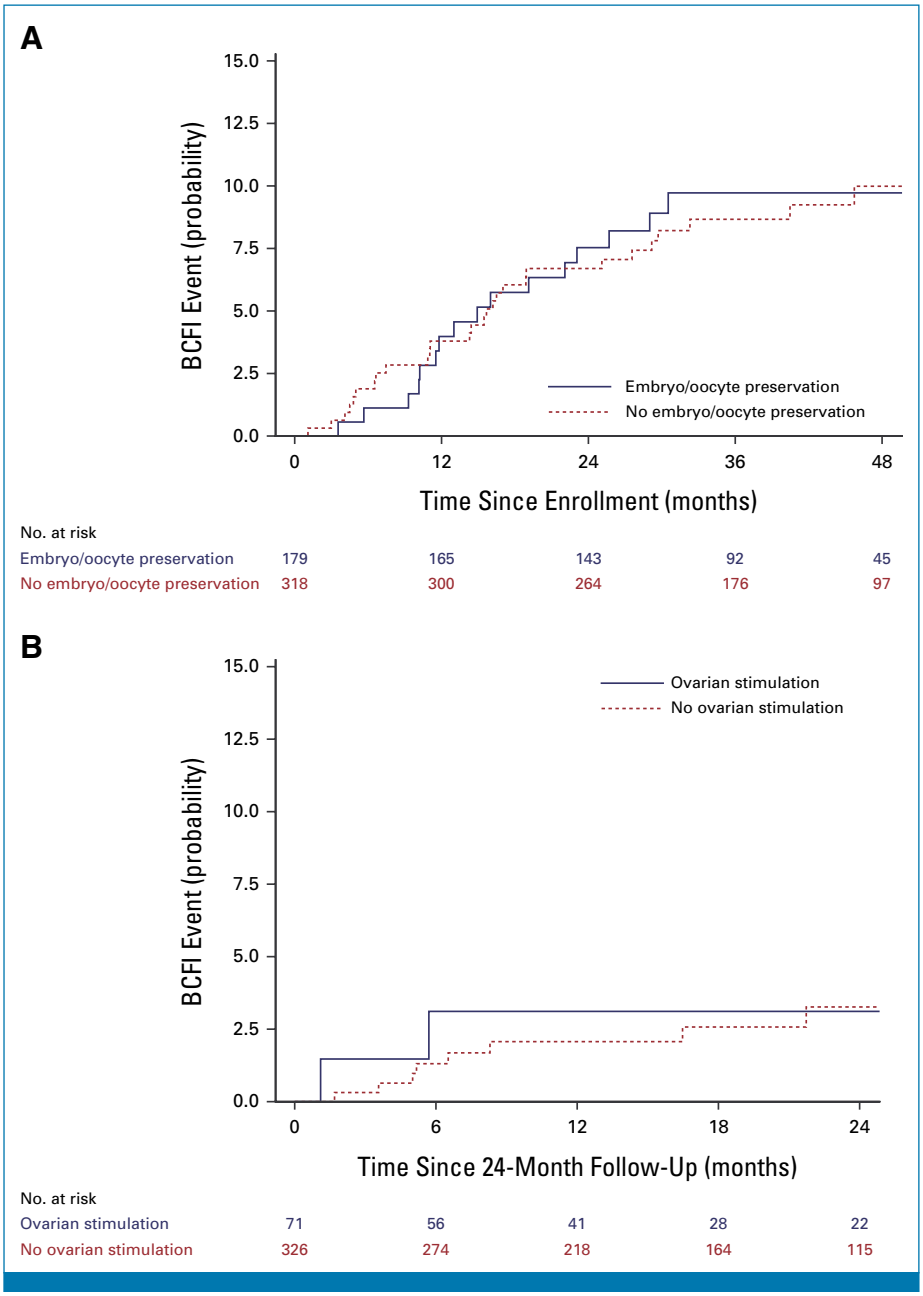

FIG 3. Cumulative incidence of breast cancer among women in the POSITIVE trial. (A) Among 497 women, by use of embryo/oocyte cryopreservation status at diagnosis (before enrollment to POSITIVE). (B) Among 397 women who are breast cancer–free with known ovarian stimulation status, and in follow-up at 24 months after enrollment (landmark analysis), by ovarian stimulation during the POSITIVE study. Ten women who had an unknown ovarian stimulation status (0 events) are not included in this figure. BCFI, breast cancer–free interval

DISCUSSION

This prespecified secondary analysis from the POSITIVE trial demonstrates that younger age is the main determinant of shorter time to pregnancy in premenopausal patients with BC temporarily interrupting adjuvant ET to attempt pregnancy. Type of ET or the use of GnRHa with chemotherapy did not appear to have an important impact. Participants who underwent cryopreserved embryo transfer during the study had higher pregnancy rates with no apparent short-term detrimental impact on prognosis. These findings are important in counseling young BC considering future pregnancy.

This study provides important insights into patterns of premature ovarian insufficiency and infertility in young patients with BC. At study entry, around 50% of patients had amenorrhea. This is not unexpected given that more than

half of the patients received GnRHa as part of adjuvant ET. Importantly, menses resumed in more than 90% of amenorrheic patients, mostly during the first 6 months. As expected, patients who did not receive chemotherapy had faster time to menstruation recovery.

The majority of patients (74%) achieved a pregnancy on study. This relatively high proportion is likely due to the inclusion of highly motivated women into the trial. While pregnancy rates were largely age-dependent, older premenopausal patients, age 40-42 years, still achieved a pregnancy rate of almost 50%. This information is highly relevant in managing the expectations of premenopausal women inquiring about their chances of future conception.

Very little is known regarding whether the type of adjuvant ET has an impact on the timing of pregnancy. This is particularly important in women who opt to temporarily interrupt ET to attempt pregnancy before completing the planned treatment duration. We found that age was the most crucial factor, with younger age associated with shorter time to pregnancy. Type of ET or menstruation status at ET interruption was not associated with time to achieve pregnancy. This suggests that future pregnancy desires should not influence the choice of ET for women considering temporary interruption to attempt pregnancy, and treatment decisions should be driven by their risk of disease recurrence and patients' tolerance.

Several ART methods were reported to be used in our study. We found that cryopreserved embryo transfer was associated with higher chances of achieving pregnancy. Nevertheless, patients who underwent IVF after enrollment still achieved a pregnancy rate of 68%, which is relatively high considering that this procedure is often considered in women who failed to achieve spontaneous pregnancy.

Ovarian stimulation either for embryo/oocyte cryopreservation at diagnosis or for IVF after enrollment entails the administration of gonadotropins for around 10-14 days, which results in increased circulating estradiol levels. In the context of hormone receptor–positive BC, concerns exist on whether such an increase could have a detrimental impact on the underlying cancer risk. Previous prospective evidence to investigate the safety of this approach comes from a small study that included 64 patients with BC with hormone receptor–positive disease who underwent embryo/oocyte cryopreservation using letrozole in combination with gonadotropins for ovarian stimulation to reduce estradiol surge.[15] Results have shown no greater risk of recurrence at 2 and 5 years, compared with 136 patients who did not undergo the same procedure.[15,16] Other studies were mostly retrospective, with a recent meta-analysis suggesting the safety of ovarian stimulation before oncologic treatment.[17] In our study, 179 patients underwent ovarian stimulation for fertility preservation at diagnosis. Outcomes were compared with those of 318 patients who did not undergo embryo/oocyte cryopreservation, to our knowledge, making it the largest prospective analysis to date to evaluate the association of ovarian stimulation on the prognosis of women with hormone receptor–positive BC. Of note, only one third of patients added letrozole to gonadotropins. Our results demonstrate no detrimental effect of ovarian stimulation with a median follow-up of 41 months, even if more patients who underwent this procedure had node-positive disease. These results are rather reassuring and relevant for fertility counseling in patients with newly diagnosed BC. Given the low number of events, it was not possible to compare the safety of the different ovarian stimulation protocols.

The use of ovarian stimulation for IVF after enrollment was also explored in our study. Available literature in this regard is mostly retrospective,[18,19] with a recent meta-analysis showing the potential safety of this approach.[17] The results of our landmark analysis at 24 months are somewhat reassuring, although inconclusive at this time as only 10 BC recurrences have been observed beyond 24 months from enrollment. Longer follow-up is required to consolidate this finding. However, the use of ovarian stimulation for IVF after having received adjuvant/neoadjuvant systemic therapy should be reserved for patients who did not undergo fertility preservation at diagnosis, which, on the basis of our results, is the most reliable way to increase future chances of pregnancy.

Our results need to be interpreted in the context of their limitations. Exact timing of ART was not available as data were captured in biannual follow-up forms completed during the 2-year period of ET interruption. This limited our ability to statistically evaluate ART use in a time-to-event analysis. In addition, data on attempts to spontaneous pregnancy before undergoing ART were not collected. We report on cumulative BCFI events at 3 years from ET interruption, which is short especially in the context of hormone receptor–positive disease. While we did not find GnRHa use with chemotherapy to be significantly associated with time to menses resumption and chance of pregnancy, we cannot draw solid conclusion on this point. This is due to the small sample size and the fact that only two thirds of patients received chemotherapy. Previous randomized studies[20,21] have shown that the concomitant administration of GnRHa with chemotherapy reduces the risk of premature ovarian insufficiency and increases the chance of menstruation resumption, with tendency of higher pregnancy rates, although for the latter, the absolute numbers remain low. In our analysis, to avoid any potential bias related to GnRHa use, analyses were adjusted to whether they were administered. Finally, although recent data among BRCA carriers suggest pregnancy after BC does not worsen disease outcomes,[22] we cannot comment on the relevance of our findings in this population, and thus, further research regarding the use of ART in BRCA-mutant patients is warranted.

In conclusion, our data provide evidence on the efficacy and short-term safety of different fertility preservation and ART options and add to the primary results of the POSITIVE trial as an important resource for the oncofertility counseling of young patients with BC.

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DISCLAIMER

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Fertility Preservation and Assisted Reproduction in Patients With Breast Cancer Interrupting Adjuvant Endocrine Therapy to Attempt Pregnancy

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APPENDIX

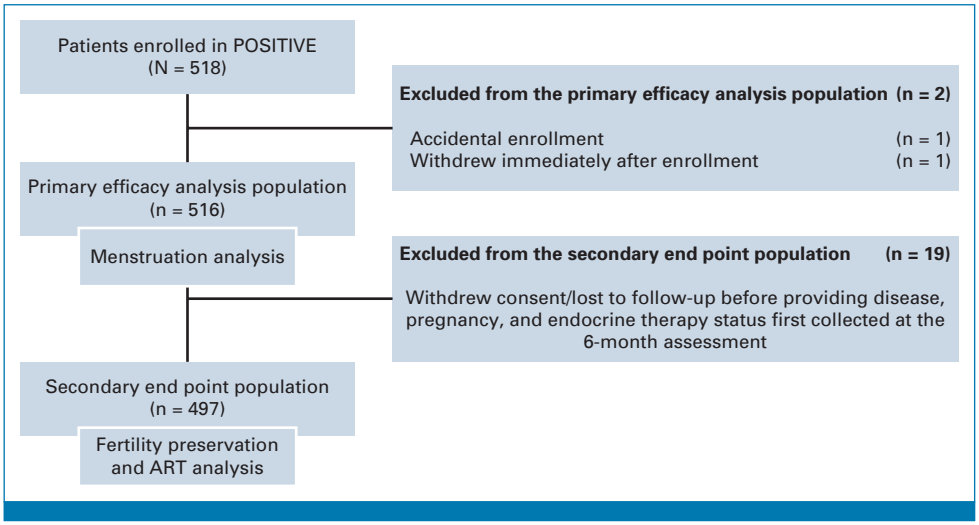

FIG A1. Patients enrolled and evaluable for analyses. ART, assisted reproductive technology.

TABLE A1. Subdistribution Hazard Ratios (sHR) for the Multivariable Fine and Gray Model for Menstruation Recovery

Variable	Point Estimate	95% LCL	95% UCL
Chemotherapy with GnRH *v* chemotherapy without GnRH	1.049	0.773	1.423
None *v* chemotherapy without GnRH	1.413	1.058	1.888
35-39 years *v* <35 years	0.963	0.732	1.267
40-42 years *v* <35 years	0.928	0.655	1.315
SERM + OFS *v* SERM only	1.242	0.764	2.019
AI + OFS *v* SERM only	1.304	0.766	2.218
Other/unknown *v* SERM only	1.313	0.598	2.879
Previous menstruation: normal *v* irregular (but continuing menstrual cycles)[a]	1.179	0.823	1.689
Previous menstruation: using hormonal contraceptives *v* irregular (but continuing menstrual cycles)[a]	1.116	0.655	1.900
HER2 status: positive *v* negative	1.199	0.877	1.638

Abbreviations: AI, aromatase inhibitor; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; LCL, lower confidence limit; OFS, ovarian function suppression; SERM, selective estrogen receptor modulator; UCL, upper confidence limit.
[a]Menstruation at breast cancer diagnosis.

TABLE A2. Multivariable Hazard Ratio Estimates of Shorter Time to Pregnancy in the Presence of Competing Risks

Variable	Point Estimate	95% LCL	95% UCL
Chemotherapy with GnRH *v* chemotherapy without GnRH	1.292	0.939	1.778
None *v* chemotherapy without GnRH	1.051	0.836	1.323
35-39 years *v* <35 years	0.742	0.590	0.932
40-42 years *v* <35 years	0.403	0.292	0.556
SERM + OFS *v* SERM only	0.938	0.709	1.240
AI + OFS *v* SERM only	0.944	0.668	1.334
Other/unknown *v* SERM only	0.854	0.577	1.263
Previous birth: yes *v* no	0.940	0.717	1.231
Menstruation at registration: irregular *v* persistent amenorrhea	1.175	0.847	1.630
Menstruation at registration: normal *v* persistent amenorrhea	1.014	0.776	1.325

Abbreviations: AI, aromatase inhibitor; GnRH, gonadotropin-releasing hormone agonist; LCL, lower confidence limit; OFS, ovarian function suppression; SERM, selective estrogen receptor modulator; UCL, upper confidence limit.