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Impact of Oncological Characteristics on Ovarian Reserve and Outcomes of the First Controlled Ovarian Stimulation Cycle in Patients with Breast Cancer

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Abstract

Objective

To evaluate the effects of histological grade, tumor stage, estrogen receptor (ER) status, triple-negative breast cancer (TNBC) status, and Ki-67 expression level on baseline ovarian reserve and the outcomes of the first controlled ovarian stimulation (COS) cycle in breast cancer patients undergoing fertility preservation, and to identify factors associated with an optimal COS outcome.

Methods

This single-center retrospective cohort study analyzed the clinical data of 67 patients with breast cancer who underwent fertility preservation at the Reproductive Medicine Center of the Third Affiliated Hospital of Zhengzhou University between January 2020 and June 2026. Patients were grouped according to histological grade (grade I vs. grades II–III), tumor stage (stage I vs. stages II–III), ER status (ER-positive vs. ER-negative), TNBC status (TNBC vs. non-TNBC), and Ki-67 expression (< 30% vs. ≥30%). An optimal COS outcome was defined as retrieval of at least 8 mature (MII) oocytes. Intergroup comparisons were performed using the Student's t-test, the Mann–Whitney U test, the chi-square test, and Fisher's exact test. Binary logistic regression was used to identify factors associated with an optimal COS outcome.

Results

Sixty-one patients were ultimately included in the analysis. The mean age was 31.51 ± 4.64 years and the mean bilateral antral follicle count (AFC) was 18.08 ± 6.10. The median body mass index (BMI) was 21.80 kg/m² (interquartile range [IQR], 20.31–23.49) and the median anti-Müllerian hormone (AMH) level was 23.70 pmol/L (IQR, 14.61–33.84). No significant differences in baseline ovarian reserve parameters or in the outcome measures of the first COS cycle were found among the oncological subgroups (all $P > 0.05$). AMH and bilateral AFC were significantly higher in patients with ≥ 8 mature oocytes than in those with < 8 mature oocytes (both $P < 0.05$). Logistic regression showed that AMH (odds ratio [OR] = 1.125, 95% confidence interval [CI] 1.046–1.210) and bilateral AFC (OR = 1.235, 95% CI 1.090–1.400) were associated with retrieval of ≥ 8 mature oocytes. With follow-up through June 2026, six patients achieved pregnancy after completion of cancer treatment, including four live births; no abnormalities in neonatal physical development were observed. The clinical pregnancy rate and live birth rate per embryo transfer cycle were 33.33% (6/18) and 22.22% (4/18), respectively.

Conclusions

In this cohort, histological grade, tumor stage, ER status, TNBC status, and Ki-67 expression level did not significantly affect ovarian reserve or the outcomes of the first COS cycle in breast cancer patients. AMH

and AFC were positively associated with the number of mature oocytes obtained.

1 Introduction

Breast cancer is one of the most common malignancies in women of reproductive age, and its age at diagnosis continues to decline. With advances in comprehensive breast cancer treatment, long-term survival has improved markedly among young patients [1], and treatment-related ovarian damage and subsequent loss of fertility have attracted increasing attention [2]. Previous studies have demonstrated that radiotherapy, chemotherapy, and endocrine therapy can cause varying degrees of ovarian reserve decline and even premature ovarian insufficiency, seriously compromising the fertility intentions and quality of life of young survivors [3, 4]. Oocyte and embryo vitrification have been shown to be safe and effective and have become key fertility preservation strategies for patients with breast cancer [5, 6].

Histological grade, tumor stage, hormone receptor expression, Ki-67 proliferation index, and molecular subtype are the principal oncological parameters used to evaluate tumor invasiveness, recurrence risk, and long-term prognosis, and they also guide the selection of subsequent treatment. Whereas the gonadotoxic effects of anticancer therapy are well recognized, it remains unclear—and the available evidence is inconsistent—whether the intrinsic biological characteristics of the tumor directly affect baseline ovarian reserve during fertility preservation cycles and, consequently, the ovarian response to exogenous gonadotropins during controlled ovarian stimulation. Sonigo et al. [7] found that the follicular output rate (FORT) differed between patients with breast cancer and those with Hodgkin lymphoma, suggesting that distinct malignancies may influence the response of antral follicles to exogenous gonadotropins. Balayla et al. [8] observed a significantly lower number of mature oocytes in patients with triple-negative breast cancer. In contrast, Grynberg et al. [9] reported that breast cancer prognostic factors—tumor grade, triple-negative status, human epidermal growth factor receptor 2 (HER2) overexpression, and high Ki-67—did not influence ovarian reserve markers or ovarian response to stimulation. In the present study, we retrospectively analyzed the clinical data of 61 patients with breast cancer who were scheduled to undergo fertility preservation at our center before initiation of cancer treatment. We aimed to evaluate the effects of oncological characteristics on baseline ovarian reserve and ovarian response to stimulation, and to identify factors associated with an optimal COS outcome, so as to inform clinical counseling and the selection of individualized stimulation protocols.

2 Materials and Methods

2.1 Study design and participants

This was a single-center retrospective cohort study. Women with breast cancer who underwent their first fertility preservation treatment at the Reproductive Medicine Center of the Third Affiliated Hospital of Zhengzhou University between January 2020 and June 2026 were assessed for eligibility.

2.2 Inclusion and exclusion criteria

The inclusion criteria were: (1) age 18–45 years; (2) histopathologically confirmed breast cancer; (3) first COS cycle, with no prior history of COS; and (4) complete clinical and laboratory data. The exclusion criteria were: (1) previous radiotherapy or chemotherapy; (2) counseling visit only, without undergoing any assisted reproductive treatment; (3) concurrent other malignancy; or (4) a history of ovarian surgery.

2.3 Groupings and data collection

All patients were classified according to five oncological characteristics: (1) histological grade I *vs.* grades II–III; (2) tumor stage I *vs.* stages II–III; (3) ER-positive *vs.* ER-negative; (4) TNBC *vs.* non-TNBC; and (5) Ki-67 < 30% *vs.* Ki-67 ≥ 30%.

Data on demographic characteristics, oncological features, ovarian reserve parameters, and COS-related variables were collected. The oncological features comprised histological grade, tumor stage, ER status, TNBC status, and Ki-67 expression level. Histological grade was assigned using the Nottingham histological grading system. Tumor stage was determined according to the 8th edition of the AJCC breast cancer staging system, which includes both anatomic and prognostic stages. The anatomic stage incorporates tumor size and extent of involvement (including skin and chest wall involvement), lymph node metastasis, and distant metastasis, whereas the prognostic stage refines and supplements the anatomic stage. Hormone receptor status was determined by immunohistochemical staining; patients with a HER2 status of 2 + underwent further testing by in situ hybridization (ISH). A Ki-67 proliferation index of 30% was used as the cutoff between low and high expression.

Ovarian reserve parameters comprised serum AMH and bilateral AFC. COS outcomes included the starting dose of gonadotropins (Gn), duration of Gn administration, total Gn dose, number of follicles ≥ 16 mm on the hCG day, total number of follicles on the hCG day, serum estradiol (E2) and progesterone (P) levels on the hCG day, number of oocytes retrieved, number of mature oocytes, oocyte maturation rate, and follicular output rate (FORT). The oocyte maturation rate was defined as the number of mature oocytes divided by the number of oocytes retrieved × 100%. FORT was defined as the number of follicles ≥ 16 mm on the hCG day divided by bilateral AFC × 100%. An optimal COS outcome was defined as retrieval of ≥ 8 mature oocytes.

For patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), embryological outcomes were calculated as follows: (1) normal 2PN fertilization rate = number of normally fertilized 2PN oocytes / total number of mature oocytes × 100%; (2) available embryo rate = number of transferable embryos / number of cleaved 2PN embryos × 100%; and (3) good-quality embryo rate = number of good-quality embryos / number of cleaved 2PN embryos × 100%.

This study was approved by the Ethics Committee of our hospital, and the requirement for informed consent was waived.

2.4 Ovarian stimulation protocols

Ovarian function was assessed according to age, basal endocrine levels on days 2–3 of the menstrual cycle, and AFC, after which a stimulation protocol was selected, principally including the GnRH antagonist protocol, the progestin-primed ovarian stimulation (PPOS) protocol, the GnRH agonist long protocol, and the mild stimulation protocol. Some patients underwent random-start ovarian stimulation. The starting Gn dose was 150–300 U/day; during stimulation, the Gn dose was maintained or adjusted in a timely manner based on ultrasound monitoring of follicular development and serum hormone levels. When at least one follicle reached ≥ 20 mm in diameter, or two to three follicles reached ≥ 18 mm, final oocyte maturation was triggered with urinary hCG (Livzon Pharmaceutical Factory, Livzon Group, Zhuhai, China), recombinant hCG (Ovidrel; Merck Serono, Switzerland), or triptorelin (Diphereline; Ipsen Pharma, France). Oocyte retrieval was performed 36–38 h after triggering. To reduce the potential risk associated with exposure to supraphysiological estrogen levels during COS, co-administration of the aromatase inhibitor letrozole (LE; Jiangsu Hengrui Pharmaceuticals, Lianyungang, China) was recommended throughout stimulation; letrozole can effectively lower circulating estrogen levels, particularly in ER-positive patients or those with an anticipated high ovarian response. The final decision regarding letrozole use was made independently by the patient after full counseling, and written informed consent was obtained.

2.5 Outcome measures and definitions

The primary outcome was the number of mature oocytes. Secondary outcomes were the total number of oocytes retrieved, the serum E2 level on the hCG day, and the number of follicles ≥ 16 mm on the hCG day. In addition, factors associated with retrieval of ≥ 8 mature oocytes were evaluated in an exploratory analysis.

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess normality and the Levene test to assess homogeneity of variance. Normally distributed continuous variables are presented as mean ± standard deviation, and intergroup comparisons were performed using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal. Skewed continuous variables are presented as median (interquartile range) and were compared using the Mann–Whitney *U* test. Categorical variables are expressed as frequency (percentage); the chi-square test was used when expected frequencies were ≥ 5 and Fisher's exact test when expected frequencies were < 5.For the intergroup comparisons across the five oncological characteristics, the Bonferroni correction was applied to control the overall type I error rate,a corrected $P < 0.0006$ was considered statistically significant. The uncorrected *P* values are retained in the tables for reference. With retrieval of ≥ 8 mature oocytes as the outcome event, a binary logistic regression model was constructed to analyze independent influencing factors. For all other analyses, $P < 0.05$ was considered statistically significant.

3 Results

Sixty-seven patients were initially screened, and 6 were excluded (4 had previously received radiotherapy or chemotherapy, 1 received counseling only without assisted reproductive treatment, and 1 had concurrent thyroid malignancy); 61 patients with breast cancer were ultimately included. Of these, 28 underwent oocyte cryopreservation, 30 underwent embryo cryopreservation, and 3 underwent both oocyte and embryo cryopreservation.

3.1 General characteristics and ovarian stimulation features

Regarding oncological characteristics, 49 patients (80.33%) had histological grade II–III tumors; 32 (52.46%) had stage I disease; 48 (78.69%) were ER-positive; 11 (18.03%) had TNBC; and 39 (63.93%) had Ki-67 ≥ 30%.With respect to ovarian stimulation features and outcomes, approximately 39.34% of patients received the GnRH antagonist protocol. The median starting Gn dose was 225.00 U (175.00, 300.00), the median duration of Gn administration was 9.00 days (8.00, 11.00), and the median total Gn dose was 2250.00 U (1725.00, 2712.50). On the hCG day, the median serum E2 level was 2425.00 pmol/L (1589.50, 3898.50) and the median P level was 4.26 nmol/L (2.65, 5.41). The median number of follicles ≥ 16 mm on the hCG day was 6.00 (5.00, 8.00), the median number of oocytes retrieved was 13.00 (8.50, 20.00), the mean number of mature oocytes was 12.16 ± 6.44, the median oocyte maturation rate was 80.00% (59.41, 95.83), and the mean FORT was 37.50% ± 15.31%.Thirty-three patients in this study ultimately underwent IVF/ICSI. In the IVF/ICSI subgroup, the overall normal 2PN fertilization rate was 80.23% (284/354), the overall available embryo rate was 89.13% (246/276), and the overall good-quality embryo rate was 60.51% (167/276). Given the limited sample size of the IVF/ICSI subgroup, no statistical comparisons by oncological characteristics were performed, and only descriptive analyses are presented.(Table 1).

Table 1
Baseline characteristics, ovarian stimulation parameters and outcomes of breast cancer patients

Item	Value
Total no. of patients	N = 61
Patient characteristics	
Age (years)	31.51 ± 4.64
BMI (kg/m²)	21.80(20.31,23.49)
Basal FSH (IU/L)	6.00(4.69,6.86)
Basal E2 (pmol/L)	162.30(112.54,291.7)
AMH (pmol/L)	23.70(14.61,33.84)
Bilateral AFC	18.08 ± 6.10
Age at menarche (years)	13.00(12.00,14.00)
Histological grade, n (%)	
Grade I	12(19.67)
Grade II-III	49(80.33)
Tumor stage, n (%)	
Stage I	32(52.46)
Stage II-III	29(47.54)
Estrogen receptor status, n (%)	
ER-positive	48(78.69)
ER-negative	13(21.31)
Triple-negative status, n (%)	
Non-TNBC	50(81.97)
TNBC	11(18.03)
Ki-67, n (%)	
< 30%	22(36.07)

Note: Normally distributed continuous variables are presented as mean ± standard deviation, skewed continuous variables as median (interquartile range), and categorical variables as frequency (%). Embryological outcomes were derived only from the 33 patients who underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI): (1) normal 2PN fertilization rate = number of normally fertilized 2PN oocytes / total number of mature oocytes × 100%; (2) available embryo rate = number of transferable embryos / number of cleaved 2PN embryos × 100%; (3) good-quality embryo rate = number of good-quality embryos / number of cleaved 2PN embryos × 100%.

Item	Value
≥ 30%	39(63.93)
Stimulation protocol, n (%)	
GnRH antagonist protocol	24(39.34)
Non-antagonist protocol	37(60.66)
Starting Gn dose (U)	225.00(175.00,300.00)
Gn duration (days)	9(8,11)
Total Gn dose (U)	2250.00(1725.00,2712.50)
Follicles ≥ 16 mm on hCG day	6.00(5.00,8.00)
Follicles on hCG day	16.00(13.00,19.50)
E2 on hCG day (pmol/L)	2425.00(1589.50,3898.50)
P on hCG day (nmol/L)	4.26(2.65,5.41)
Oocytes retrieved	13.00(8.50,20.00)
Mature oocytes	12.16 ± 6.44
Oocyte maturation rate (%)	80.00(59.41,95.83)
FORT (%)	37.50 ± 15.31
Embryological outcomes	
IVF/ICSI patients, n	N = 33
Normal 2PN fertilization rate (%)	80.23(284/354)
Available embryo rate (%)	89.13(246/276)
Good-quality embryo rate (%)	60.51(167/276)

Note: Normally distributed continuous variables are presented as mean ± standard deviation, skewed continuous variables as median (interquartile range), and categorical variables as frequency (%). Embryological outcomes were derived only from the 33 patients who underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI): (1) normal 2PN fertilization rate = number of normally fertilized 2PN oocytes / total number of mature oocytes × 100%; (2) available embryo rate = number of transferable embryos / number of cleaved 2PN embryos × 100%; (3) good-quality embryo rate = number of good-quality embryos / number of cleaved 2PN embryos × 100%.

3.2 Comparisons of baseline characteristics and COS outcomes by oncological characteristic

In the analysis based on histological grade, no significant difference in the number of mature oocytes retrieved was observed between grade I and grade II–III patients ($P = 0.694$). The total number of

oocytes retrieved, the serum E2 level on the hCG day, and the number of follicles ≥ 16 mm on the hCG day likewise showed no differences between the two groups (all $P > 0.05$).(Table 2).

Table 2
Comparison of baseline characteristics and ovarian stimulation outcomes between breast cancer patients with histological grade Ⅰ and grade Ⅱ-Ⅲ

Item	Grade I	Grades II–III	t/Z value	P value
No. of patients	12	49		
Age (years)	33.00 ± 4.09	31.14 ± 4.74	1.248	0.572
BMI (kg/m²)	21.30(20.11,24.30)	22.10(20.31,23.49)	-0.218	0.828
Basal FSH (IU/L)	6.22(4.77,7.04)	5.92(4.29,6.84)	-0.708	0.479
Basal E2 (pmol/L)	152.55(92.80,223.60)	171.6(115.61,298.20)	-1.143	0.253
AMH (pmol/L)	20.95(10.11,43.61)	23.70(16.17,33.47)	-0.254	0.799
Bilateral AFC	17.67 ± 7.43	18.18 ± 5.82	-0.261	0.472
Age at menarche (years)	13.00(13.00,14.00)	13.00(12.00,14.00)	-1.409	0.159
Starting Gn dose (U)	262.50(156.25,300.00)	225.50(175.00,300.00)	-0.637	0.524
Gn duration (days)	8.50(8.00,11.00)	10.00(8.00,11.00)	-0.874	0.382
Total Gn dose (U)	2400.00(1443.75,3000.00)	2162.50(1800.00,2700.00)	-0.036	0.971
Follicles ≥ 16 mm on hCG day	5.50(3.50,8.00)	6.00(5.00,7.00)	-0.650	0.515
Follicles on hCG day	19.50 ± 9.87	15.90 ± 5.87	1.213	< 0.05
E2 on hCG day (pmol/L)	2296.50(1303.00,4622.50)	2562.00(1706.00,3508.00)	-0.599	0.549
P on hCG day (nmol/L)	4.72(1.91,6.10)	4.01(2.99,4.95)	-0.200	0.842
Oocytes retrieved	15.92 ± 9.42	13.96 ± 7.42	0.776	0.124

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	Grade I	Grades II–III	t/Z value	P value
Mature oocytes	11.92 ± 5.90	12.22 ± 6.62	-0.147	0.694
Oocyte maturation rate (%)	85.42(78.89,100.00)	100.00(81.82,100.00)	-0.802	0.422
FORT (%)	34.31(23.23,41.67)	38.89(26.32,46.67)	-0.808	0.419

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

In the analysis based on tumor stage, stage I patients had more follicles ≥ 16 mm on the hCG day than stage II–III patients (7.00 *vs.* 6.00, $P < 0.05$); however, no significant differences were observed in the serum E2 level on the hCG day, the number of mature oocytes, or the total number of oocytes retrieved (all $P > 0.05$).(Table 3).

Table 3
Comparison of baseline characteristics and ovarian stimulation outcomes between breast cancer patients with tumor stage Ⅰ and stage Ⅱ-Ⅲ

Item	Stage I	Stages II–III	t/Z value	P value
No. of patients	32	29		
Age (years)	31.41 ± 4.15	31.62 ± 5.21	−0.179	0.218
BMI (kg/m²)	*21.98(19.90,23.69)*	21.72(20.36,23.10)	−0.123	0.902
Basal FSH (IU/L)	5.73(4.27,6.51)	6.23(5.64,7.36)	−1.719	0.086
Basal E2 (pmol/L)	163.35(116.40,383.60)	162.30(111.30,286.40)	−0.679	0.497
AMH (pmol/L)	25.48(16.81,33.74)	23.67(11.43,33.67)	−0.729	0.466
Bilateral AFC	18.00(14.50,22.00)	18.00(11.00,24.00)	−0.261	0.794
Age at menarche (years)	13.00(12.00,14.00)	13.00(12.00,14.00)	−0.333	0.739
Starting Gn dose (U)	206.25(150.00,262.50)	225.00(205.00,300.00)	−1.864	0.062
Gn duration (days)	9.00(8.00,11.00)	10.00(8.00,11.00)	−0.337	0.736
Total Gn dose (U)	2282.81 ± 761.62	2393.09 ± 824.14	−0.543	0.421
Follicles ≥ 16 mm on hCG day	7.00(5.00,8.50)	6.00(5.00,7.00)	−2.115	< 0.05
Follicles on hCG day	17.22 ± 7.22	15.93 ± 6.57	0.726	0.629
E2 on hCG day (pmol/L)	2533.50(1481.50,4510.50)	2425.00(1706.00,3466.00)	−0.137	0.891
P on hCG day (nmol/L)	4.39(2.88,5.60)	3.90(2.56,4.95)	−0.729	0.466

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	Stage I	Stages II–III	t/Z value	P value
Oocytes retrieved	13.50(9.00,22.00)	11.00(8.00,18.00)	−1.049	0.294
Mature oocytes	11.50(8.00,15.50)	11.00(6.00,17.00)	−0.311	0.756
Oocyte maturation rate (%)	90.42(78.47,100.00)	100.00(87.50,100.00)	−1.154	0.248
FORT (%)	38.89(27.64,48.68)	32.00(25.00,44.44)	−1.185	0.236

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

In the analysis based on estrogen receptor status, no differences were observed between ER-negative and ER-positive patients in serum E2 on the hCG day, the number of follicles ≥ 16 mm on the hCG day, the number of mature oocytes, or the total number of oocytes retrieved (all $P > 0.05$) (Table 4).

Table 4
Comparison of baseline characteristics and ovarian stimulation outcomes between ER-negative and ER-positive breast cancer patients

Item	ER-negative	ER-positive	t/Z value	P value
No. of patients	13	48		
Age (years)	30.23 ± 3.59	31.85 ± 4.86	−1.121	0.051
BMI (kg/m²)	21.93 ± 1.62	22.14 ± 3.19	−0.226	0.079
Basal FSH (IU/L)	5.40(4.04,6.18)	6.19(4.96,6.91)	−1.594	0.111
Basal E2 (pmol/L)	171.60(128.50,240.00)	158.70(112.54,295.25)	−0.159	0.874
AMH (pmol/L)	18.20(15.10,25.97)	25.88(14.63,36.89)	−1.647	0.100
Bilateral AFC	16.31 ± 5.91	18.56 ± 6.13	−1.186	0.962
Age at menarche (years)	13.00(12.00,13.00)	13.00(12.00,14.00)	−0.887	0.375
Starting Gn dose (U)	200.00(150.00,225.00)	225.00(190.00,300.00)	−1.164	0.245
Gn duration (days)	10.00(9.00,11.00)	9.00(8.00,11.00)	−0.795	0.427
Total Gn dose (U)	2150.00(1687.50,2700.00)	2250.00(1775.00,2712.50)	−0.159	0.874
Follicles ≥ 16 mm on hCG day	7.00(4.00,7.00)	6.00(5.00,8.00)	−0.107	0.915
Follicles on hCG day	14.15 ± 5.27	17.27 ± 7.17	−1.460	0.187
E2 on hCG day (pmol/L)	2425.00(1905.00,2994.00)	2487.00(1548.50,4306.50)	−0.035	0.972
P on hCG day (nmol/L)	3.81(3.11,4.72)	4.29(2.55,5.82)	−0.564	0.573

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	ER-negative	ER-positive	t/Z value	P value
Oocytes retrieved	12.00(9.00,15.00)	14.00(8.50,21.50)	−1.217	0.224
Mature oocytes	9.00(6.00,13.00)	11.00(7.50,17.00)	−1.271	0.204
Oocyte maturation rate (%)	100.00(66.67,100.00)	94.58(82.58,100.00)	−0.216	0.829
FORT (%)	38.97 ± 16.29	37.10 ± 15.19	0.389	0.800

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Compared with non-TNBC patients, TNBC patients showed similar serum E2 levels on the hCG day, numbers of follicles ≥ 16 mm on the hCG day, numbers of mature oocytes, and total numbers of oocytes retrieved (all $P > 0.05$) (Table 5).

Table 5
Comparison of baseline characteristics, ovarian stimulation parameters and outcomes between non-TNBC and TNBC breast cancer patients

Item	Non-TNBC	TNBC	t/Z value	P value
No. of patients	50	11		
Age (years)	31.84 ± 4.77	30.00 ± 3.82	1.194	0.104
BMI (kg/m²)	21.91(20.31,23.56)	21.80(21.15,23.32)	-0.188	0.851
Basal FSH (IU/L)	6.10(4.81,6.88)	5.40(4.01,6.28)	-1.248	0.212
Basal E2 (pmol/L)	158.70(111.30,233.10)	171.60(133.90,233.10)	-0.356	0.722
AMH (pmol/L)	25.88(14.12,35.80)	18.20(15.91,25.06)	-1.538	0.124
Bilateral AFC	18.52 ± 6.15	16.09 ± 5.75	1.200	0.712
Age at menarche (years)	13.00(12.00,14.00)	13.00(12.00,13.50)	-0.581	0.561
Starting Gn dose (U)	225.00(180.00,300.00)	200.00(162.50,225.00)	-1.182	0.237
Gn duration (days)	9.00(8.00,11.00)	9.00(9.00,10.50)	-0.304	0.761
Total Gn dose (U)	2250.00(1750.00,2725.00)	2150.00(1700.00,2700.00)	-0.385	0.700
Follicles ≥ 16 mm on hCG day	6.00(5.00,8.00)	7.00(3.50,7.00)	-0.616	0.538
Follicles on hCG day	16.00(13.00,22.00)	14.00(10.50,17.50)	-1.222	0.222
E2 on hCG day (pmol/L)	2608.50(1565.00,4331.00)	2391.00(1759.50,2986.50)	-0.647	0.518
P on hCG day (nmol/L)	4.29(2.54,5.93)	3.81(3.25,4.72)	-0.525	0.599
Oocytes retrieved	14.00(9.00,21.00)	12.00(7.50,14.00)	-1.184	0.237

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	Non-TNBC	TNBC	t/Z value	P value
Mature oocytes	11.00(8.00,17.00)	9.00(6.00,13.00)	-1.334	0.182
Oocyte maturation rate (%)	94.58(83.33,100.00)	100.00(66.67,100.00)	-0.420	0.675
FORT (%)	37.65 ± 15.75	36.79 ± 13.77	0.167	0.707

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

In the analysis based on the Ki-67 proliferation index, the low Ki-67 group had more follicles ≥ 16 mm on the hCG day than the high Ki-67 group (7.00 *vs.* 6.00, $P < 0.05$), whereas the serum E2 level on the hCG day, the number of mature oocytes, and the total number of oocytes retrieved showed no statistically significant differences (all $P > 0.05$).(Table 6).

After Bonferroni correction of all intergroup comparison indicators across the five oncological characteristics, the uncorrected differences in the number of follicles ≥ 16 mm on the hCG day according to tumor stage and Ki-67 expression level were no longer statistically significant.

Table 6
Comparison of baseline characteristics and ovarian stimulation outcomes between breast cancer patients with low Ki-67 expression and high Ki-67 expression

Item	Ki-67 < 30%	Ki-67 ≥ 30%	t/Z value	P value
No. of patients	22	39		
Age (years)	32.64 ± 3.95	30.87 ± 4.93	1.438	0.687
BMI (kg/m²)	*21.97(20.20*,24.39*)*	21.80(20.34,23.31)	-0.496	0.620
Basal FSH (IU/L)	5.85(4.75,6.69)	6.15(4.72,6.86)	-0.563	0.573
Basal E2 (pmol/L)	208.80(124.78,412.90)	154.90(111.20,271.75)	-1.232	0.218
AMH (pmol/L)	31.15(21.85,38.10)	19.22(13.90,29.53)	-1.795	0.073
Bilateral AFC	19.64 ± 5.90	17.21 ± 6.11	1.510	0.615
Age at menarche (years)	13.50(12.00,14.00)	13.00(12.00,14.00)	-1.285	0.199
Starting Gn dose (U)	225.00(175.00,300.00)	225.00(175.00,300.00)	-0.310	0.756
Gn duration (days)	8.50(8.00,10.00)	10.00(9.00,11.00)	-1.706	0.286
Total Gn dose (U)	2250.00(1600.00,2475.00)	2162.50(1838.75,2750.00)	-1.067	0.286
Follicles ≥ 16 mm on hCG day	7.00(6.00,9.00)	6.00(4.50,7.00)	-2.313	< 0.05
Follicles on hCG day	19.09 ± 7.38	15.21 ± 6.27	2.180	0.341
E2 on hCG day (pmol/L)	2795.50(1710.00,4722.00)	2412.00(1589.50,3360.00)	-1.081	0.280
P on hCG day (nmol/L)	4.49(2.99,6.50)	3.90(2.54,4.93)	-1.307	0.191
Oocytes retrieved	18.23 ± 8.38	12.15 ± 6.61	3.125	0.096

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	Ki-67 < 30%	Ki-67 ≥ 30%	t/Z value	P value
Mature oocytes	14.41 ± 6.61	10.90 ± 6.07	2.103	0.904
Oocyte maturation rate (%)	87.32(79.17,100.00)	100.00(85.71,100.00)	-0.904	0.366
FORT (%)	38.19(28.00,54.55)	33.33(25.00,43.65)	-1.134	0.257

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

3.3 Comparisons of baseline characteristics and COS outcomes by number of mature oocytes

Using 8 mature oocytes (MII oocytes) as the cutoff, 17 patients yielded < 8 MII oocytes and 44 patients yielded ≥ 8 MII oocytes. Univariable intergroup comparisons indicated that the ≥ 8 MII group was younger than the < 8 MII group (31.00 *vs.* 32.82 years, $P = 0.041$) and had significantly higher AMH and AFC levels ($P < 0.05$); no significant between-group differences were found in BMI, basal hormone levels, age at menarche, histological grade, tumor stage, ER status, TNBC status, or Ki-67 expression.(Table 7).

Table 7
Comparison of baseline characteristics and ovarian stimulation outcomes in breast cancer patients grouped according to the number of MII oocytes

Item	< 8 MII oocytes	≥ 8 MII oocytes	χ^2/Z value	P value
No. of patients	17	44		
Age (years)	32.82 ± 5.98	31.00 ± 3.98	1.162	0.041
BMI (kg/m²)	22.40 ± 2.06	21.97 ± 3.20	0.509	0.197
Basal FSH (IU/L)	5.76(4.24,6.84)	6.03(4.77,6.82)	1.305	0.150
Basal E2 (pmol/L)	116.30(115.61,298.20)	163.00(112.54,273.20)	-0.012	0.857
AMH (pmol/L)	12.98(6.54,22.77)	28.28(17.91,38.04)	-4.648	0.001
Bilateral AFC	12.00(9.00,19.00)	19.50(15.50,24.00)	-3.404	0.001
Age at menarche (years)	13.00(13.00,14.00)	13.00(12.00,14.00)	-0.937	0.349
Histological grade, n (%)			Fisher	0.723
Grade I	4	8		
Grade II/III	13	36		
Tumor stage, n (%)			0.276	0.600
Stage I	8	24		
Stage II/III	9	20		
Estrogen receptor status, n (%)			Fisher	0.486
ER-positive	12	36		
ER-negative	5	8		
Triple-negative status, n (%)			Fisher	0.263
Non-TNBC	12	38		
TNBC	5	6		

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

Item	< 8 MII oocytes	≥ 8 MII oocytes	χ^2/Z value	P value
Ki-67, n (%)			3.467	0.063
< 30%	3	19		
≥ 30%	14	25		

Note: Normally distributed continuous variables are presented as mean ± standard deviation and compared between groups using the independent samples *t*-test, with Welch's corrected *t*-test used when variances were unequal; skewed continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney *U* test; categorical variables are expressed as frequency (%).

The relevant variables were entered into a binary logistic regression model, which showed that AMH (OR = 1.125, 95% CI 1.046–1.210, $P < 0.05$) and AFC (OR = 1.235, 95% CI 1.090–1.400, $P < 0.05$) were favorable factors for obtaining ≥ 8 MII oocytes; none of the remaining breast cancer oncological characteristics was associated with the outcome (all $P > 0.05$).(Table 8).

Table 8
Binary logistic regression analysis for factors associated with obtaining ≥ 8 MII oocytes

Item	OR	95%CI	P value
Age (years)	0.916	0.807–1.039	0.172
AMH (pmol/L)	1.125	1.046–1.210	< 0.05
Bilateral AFC	1.235	1.090–1.400	< 0.05
Histological grade (I / II–III)	0.722	0.186–2.807	0.638
Tumor stage (I / II–III)	0.600	0.440–4.146	0.600
ER status (negative / positive)	1.875	0.514–6.841	0.341
Non-TNBC / TNBC	0.379	0.098–1.466	0.160
Ki-67 (< 30% / ≥30%)	0.282	0.071–1.123	0.073

Note: A binary logistic regression model was used, with the dependent variable defined as retrieval of ≥ 8 mature oocytes (0 = no, 1 = yes). OR, odds ratio; $P < 0.05$ was considered statistically significant.

With follow-up through June 2026, six patients pursued pregnancy after completion of cancer treatment, including four live births, and no abnormalities in neonatal physical development were observed. The clinical pregnancy rate per embryo transfer cycle was 33.33% (6/18) and the live birth rate was 22.22% (4/18).

4 Discussion

This study systematically investigated the effects of breast cancer histological grade, tumor stage, hormone receptor status, TNBC subtype, and Ki-67 proliferation index on baseline ovarian reserve and first-cycle COS outcomes in patients undergoing fertility preservation. Overall,none of the above oncological characteristics significantly affected the patients' ovarian reserve levels, number of oocytes retrieved, or number of mature oocytes; only patients with stage I tumors or low Ki-67 expression showed a modestly higher number of follicles ≥ 16 mm on the hCG day, but this difference did not translate into differences in ultimate stimulation outcomes such as the number of oocytes retrieved, number of mature oocytes, oocyte maturation rate, or FORT.

Previous studies in the oncofertility population have reported a cumulative live birth rate of 35.8% (95% CI 14.3–57.2) when 8 mature oocytes are obtained [10, 11]; accordingly, the present study defined ≥ 8 mature oocytes as an optimal COS outcome. The grouped analyses showed that the ≥ 8 MII group had significantly higher baseline AMH (28.28 *vs.* 12.98 pmol/L, $P = 0.001$) and significantly higher bilateral AFC (19.50 *vs.* 12.00, $P = 0.001$), and binary logistic regression further confirmed that AMH (OR = 1.125, 95% CI 1.046–1.210) and bilateral AFC (OR = 1.235, 95% CI 1.090–1.400) were favorable factors for obtaining ≥ 8 MII oocytes.

This finding is consistent with the large cohort study by Wald *et al.* [12], which included 267 breast cancer patients and found, after adjusting for age, BMI, and baseline AFC, that the total number of oocytes retrieved and the number of mature oocytes were not affected by tumor stage or grade. Grynberg *et al.* [9] likewise demonstrated that breast cancer tumor grade, TNBC, HER2 overexpression, and high Ki-67 did not affect ovarian reserve markers or ovarian response to stimulation. However, Volodarsky-Perel *et al.* [13] reached a different conclusion: in 155 breast cancer patients, the high-grade group (G3) had a significantly lower number of mature oocytes than the low-grade group (G1–2) (7 *vs.* 13, $P = 0.0002$) and also had fewer frozen embryos (3 *vs.* 5, $P = 0.02$), whereas mature oocyte numbers did not differ significantly in the analysis by tumor stage (8 *vs.* 9, $P = 0.06$). The same group had previously reported, in a study including multiple malignancies, that low grade was associated with better fertility preservation outcomes (OR = 4.26, 95% CI 1.82–9.98, $P = 0.0009$) [14]. These inconsistencies may arise from differences in ovarian stimulation protocols, ethnicity, and sample size, among other factors. In the present study, the median total Gn dose in the high-grade group was in fact slightly lower than that in the low-grade group (2162.5 *vs.* 2400 U), and baseline AFC and AMH were comparable between the two groups, suggesting that the influence of histological grade on ovarian reserve was not apparent in this cohort.

The present study showed no significant differences in the number of mature oocytes between ER-positive and ER-negative patients or between TNBC and non-TNBC patients. Yahyaei *et al.* [15], in a study of 128 breast cancer patients, reported that ER, PR, TNBC, and Ki-67 status did not affect ovarian response to stimulation. The retrospective cohort study by Balayla *et al.* [8] reported that the TNBC group had significantly fewer mature oocytes than ER/PR-positive patients (7 *vs.* 9, $P = 0.02$), and further analysis indicated that TNBC was an independent adverse factor for obtaining ≥ 10 mature oocytes (OR = 0.41, 95% CI 0.19–0.92). Notably, although the difference was not statistically significant in the present

study, the TNBC group showed a trend toward a lower number of mature oocytes, and AMH levels also tended to be lower in the TNBC group (18.20 *vs.* 25.88 pmol/L, $P = 0.124$). This phenomenon echoes the findings of Raad *et al.* [16], who included 321 breast cancer patients treated with in vitro maturation and found that AMH levels were significantly lower in the TNBC group than in the ER/PR/HER2-positive group (3.1 *vs.* 4.0 ng/mL, $P = 0.02$). Previous epidemiological data indicate that the prevalence of *BRCA* mutations in the TNBC population can reach 10%–30% [17–19]. The study by Oktay *et al.* [20] showed that *BRCA* mutation carriers had a significantly higher poor ovarian response rate than non-carriers (33.3 *vs.* 3.3%, $P = 0.014$), which can cause occult primary ovarian insufficiency and an intrinsically weaker ovarian reserve and stimulation response in this population.Combining the findings of Raad *et al.* [16], a plausible hypothesis can be formulated that the influence of TNBC on ovarian reserve is mediated mainly by *BRCA* mutations rather than by a direct effect of tumor cells. The meta-analysis by Turan *et al.* [21] showed that AMH levels in *BRCA1* mutation carriers were approximately 33% lower than in control populations ($P = 0.004$). In the present study, AMH was approximately 30% lower in the TNBC group than in the non-TNBC group, a magnitude highly consistent with the results of Turan *et al.*, providing indirect support for this hypothesis.

In the present study, the low Ki-67 group had more follicles ≥ 16 mm on the hCG day than the high Ki-67 group (7.00 *vs.* 6.00, $P < 0.05$), but this difference did not translate into benefits in the numbers of oocytes or mature oocytes. A prospective study in 2025 was the first to analyze the correlation between the Ki-67 proliferation index and the number of mature oocytes and found no significant linear trend [22]. Yahyaei *et al.* [15] likewise found no influence of Ki-67 expression status on the numbers of oocytes retrieved or mature oocytes. We speculate that tumor proliferative activity mainly affects the synchrony of follicular development rather than the total reserve of the follicular pool. High Ki-67 expression reflects active tumor cell proliferation and may mildly suppress granulosa cell proliferation through systemic chronic inflammatory factors (such as IL-6 and TNF-α), leading to delayed dominant follicle recruitment and asynchronous development; however, the total size of the antral follicle pool is determined by baseline ovarian reserve (AMH/AFC) and was not affected by tumor characteristics, and consequently no significant differences emerged in the total number of oocytes retrieved or the oocyte maturation rate. At present, no consensus guideline defines a cutoff for high versus low Ki-67 expression; this study exploratorily used 30% as the boundary between low and high Ki-67 expression, and validation with large-sample data is still required in the future.

The results of this study indicate that histological grade, tumor stage, molecular subtype, and Ki-67 expression level in breast cancer should not serve as grounds for excluding patients from fertility preservation; in clinical decision-making, there is no need to presume a poor ovarian response simply because a patient has TNBC, a high grade, or high Ki-67, nor to deliberately increase the starting Gn dose. For patients with TNBC, routine germline BRCA genetic testing is recommended, and mutation carriers may consider a dual cryopreservation strategy combining oocyte and embryo freezing. AMH and AFC are the core basis for protocol formulation and dose adjustment. Lee et al. [23] reported that AMH and AFC are relatively reliable markers for predicting outcomes of oocyte/embryo cryopreservation cycles in breast cancer patients, and that the probability of poor ovarian response was significantly

increased when AMH ≤ 1.2 ng/mL (P < 0.05). FORT reflects the sensitivity of antral follicles to exogenous follicle-stimulating hormone (FSH) and can indirectly indicate the potential for follicular development and maturation. A previous study of 322 patients undergoing IVF-embryo transfer found that clinical pregnancy rates increased with higher FORT (P < 0.003) [24]. In a comparison of breast cancer and Hodgkin lymphoma patients, Sonigo et al. [7] found that FORT was significantly higher in breast cancer patients (39.8% vs. 27.0%, P = 0.004), suggesting that different malignancies differ in their effects on the response to exogenous FSH. For patients with a low AFC who still wish to conceive, a high FORT suggests that the developmental potential of residual follicles is acceptable and that an ideal number of mature oocytes may still be obtained. In addition, serum E2 levels on the hCG day did not differ significantly among the oncological subgroups in this study, confirming that stimulation protocols combined with letrozole can effectively control estrogen exposure. Fertility preservation counseling should be provided as early as possible to all women of reproductive age newly diagnosed with breast cancer, regardless of their oncological characteristics.

In summary, the oncological characteristics of breast cancer did not affect patients' baseline ovarian reserve or first-cycle stimulation outcomes, and AMH and AFC were the core predictors of ovarian response. Future multicenter prospective cohort studies are needed to enlarge the sample sizes of the TNBC and BRCA-mutation subgroups, to combine follicular fluid inflammatory markers and granulosa cell function testing to clarify the mechanisms by which tumor proliferative activity regulates follicular developmental synchrony, and to conduct long-term follow-up of tumor recurrence and offspring health outcomes, so as to provide higher-level evidence for the clinical practice of fertility preservation in breast cancer patients.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Third Affiliated Hospital of Zhengzhou University and performed in accordance with the principles of the Declaration of Helsinki(Approval No. 2026-330-01).Given the retrospective observational design of this study, and that all clinical data were fully de-identified and anonymized prior to analysis with no traceable personal identifiable information, the Ethics Committee formally approved the waiver of written informed consent for all included patients. All data were used exclusively for this academic research and did not impose any additional risk to the rights and interests of the patients.

Clinical trial number

not applicable.

Competing interests

This article does not involve any conflict of competing interest.

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Author Contribution

Jiaheng Li: Study design and research implementation;Yueling Yang:Data collection and manuscript drafting;Yue Mao Mengyuan Zhang: Data collection; Yichun Guan: Study supervision; Yanli Liu: Data analysis;Jing Li: Statistical methodology guidance;Qi Jia: Clinical expertise and support Shanshan Du:Technical and material support.All authors revised the article and gave their final approval of the submitted version.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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