Title
Breast cancer grade and stage do not affect fertility preservation outcomes

Journal
Journal of Assisted Reproduction and Genetics, 39(5)

ISSN
1058-0468

Authors
Wald, Kaitlyn
Wang, Ange
Abel, Mary Kathryn
et al.

Publication Date
2022-05-01

DOI
10.1007/s10815-022-02473-5

Peer reviewed

Journal of Assisted Reproduction and Genetics (2022) 39:1155–1161
https://doi.org/10.1007/s10815-022-02473-5

FERTILITY PRESERVATION

Breast cancer grade and stage do not affect fertility preservation outcomes

Kaitlyn Wald[1] · Ange Wang[1] · Mary Kathryn Abel[1,2] · Jerrine Morris[1] · Joseph M. Letourneau[1,3] · Evelyn Mok-Lin[1] · Marcelle I. Cedars[1] · Mitchell P. Rosen[1]

Received: 13 January 2022 / Accepted: 16 March 2022 / Published online: 23 March 2022

Abstract

Purpose To investigate if breast cancer stage and grade affect fertility preservation outcomes.

Methods We performed a retrospective cohort study that included premenopausal women with breast cancer undergoing fertility preservation diagnosed between January 2011 and January 2019. The primary outcome measure was the number of mature oocytes (MII) per antral follicle count (AFC). Secondary outcome measures included total oocytes retrieved, total mature oocytes retrieved, and greater than 10 mature oocytes preserved. Univariate and multivariate models were used to assess the association of low vs. high stage (low stage I–II and high stage III–IV) and grade I vs. grade II/III with each outcome, with adjustment for confounders.

Results A total of 267 premenopausal breast cancer patients undergoing fertility preservation were included in our study, with the majority presenting with low stage ($N=215$, 80.5%), grade II/III ($N=235$, 88.1%) disease. Baseline AFC, total gonadotropin dose, days of stimulation, and follicles ≥ 13 mm on the day of trigger did not differ by stage or grade. After adjusting for age, BMI, and baseline AFC, we found that the mean MII per AFC did not differ by stage (1.0 vs. 1.1, $P=0.3$) or grade (1.0 vs. 1.0, $P=0.92$). Similarly, total oocytes retrieved, total MII retrieved, and percentage of patients who were able to preserve greater than 10 MII did not differ by breast cancer stage or grade (all $P>0.2$).

Conclusion Breast cancer grade and stage do not impact ovarian stimulation or fertility preservation outcome.

Keywords Fertility preservation · Breast cancer · Cancer grade · Cancer stage

Introduction

In the USA, a total of 10,000 to 15,000 new cases of breast cancer are diagnosed in women under 40 years of age each year [1]. Advances in treatment, particularly in chemotherapeutic agents, have significantly improved long-term survival outcomes for cancer patients [1]. However, chemotherapy has well-documented gonadotoxic effects, prompting national organizations, including the American Society of Clinical Oncology and American Society of Reproductive Medicine, to recommend all reproductive-aged women be counseled on the impact of these treatments on future fertility and options for fertility preservation prior to cancer treatment [2, 3]. Cryopreservation of oocytes and embryos has been accepted as the standard of care in oncology and reproductive medicine. Evidence suggests that fertility preservation can be completed without significant delays in cancer treatment, impact on disease-free survival, or likelihood of cancer recurrence for most cancers [4–7].

Although fertility preservation may not substantially influence cancer outcomes in reproductive-aged women, it is less clear how cancer impacts fertility preservation outcomes. As a systemic illness, it is plausible that cancer can impact fertility even prior to treatment. In fact, studies have shown decreased sperm counts present in men with Hodgkin's lymphoma and testicular cancer before

Kaitlyn Wald and Ange Wang are joint first authors.

✉ Ange Wang
ange.wang@ucsf.edu

[1] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, 499 Illinois Street, 6th Floor, CA 94158 San Francisco, USA

[2] School of Medicine, University of California, San Francisco, 533 Parnassus Avenue, San Francisco, CA 94143, USA

[3] Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, USA

undergoing gonadotoxic treatment [8–12]. In contrast, a meta-analysis of high-quality studies found that ovarian stimulation outcomes are not impacted by breast cancer diagnosis; however, the associations between fertility outcomes and cancer severity, like stage and grade, were not assessed in detail [13]. Interestingly, a recent report consisting of 147 women with a variety of cancers found that a higher grade of cancer was associated with fewer retrieved mature oocytes and cryopreserved embryos [14]. While this study is the largest to date to assess the impact of cancer grade and stage on fertility preservation outcomes, its heterogeneity (with multiple cancer types) and small cohort make it challenging to draw conclusions about cryopreservation outcomes by specific cancer subtype. As such, more robust studies of women undergoing fertility preservation by cancer type are needed. Another study of 155 Canadian breast cancer patients by the same author group found higher breast cancer grade (but not stage) was associated with a lower number of mature oocytes and embryos cryopreserved [15]. In this cohort study, we assess the impact of stage and grade on fertility preservation outcomes in 267 patients diagnosed with breast cancer, one of the most common types of cancer diagnosed in women of reproductive age [1].

Materials and methods

Study population

A retrospective chart review was completed to identify patients diagnosed with breast cancer who underwent fertility preservation at the Center for Reproductive Health at the University of San Francisco between January 2011 and January 2019. Inclusion criteria for this study included the following: premenopausal state, age 18 to 45 years, and newly diagnosed breast cancer undergoing fertility preservation prior to gonadotoxic treatment. Patients were excluded if they were older than 45 years, lacked cancer stage or grade information, or underwent chemotherapy or radiation prior to fertility preservation.

Breast cancer stage and grade were obtained by chart review. Breast cancer stage was determined clinically for those undergoing neoadjuvant chemotherapy and by surgical pathology for all other patients. The Tumor, Node, Metastasis (TNM) staging system for breast cancer was used. Specifically, stage I and II cancers were classified as a low-stage disease, while stage III and IV were classified as a high-stage disease. Breast cancer grade was also obtained through chart review of pathology reports and assigned using the Elston-Ellis grading system [16], and was stratified by grade I versus grade II/III in our analysis.

Stimulation protocol

All patients underwent either oocyte or embryo cryopreservation. A combined recombinant follicle-stimulating hormone (FSH) and human menopausal gonadotropins (hMG) antagonist-based, random-start, ovarian stimulation protocol was used for all patients. Patients with estrogen receptor (ER)–positive breast cancer were co-treated with letrozole or tamoxifen during stimulation. Trigger was standardly completed with human chorionic gonadotropin (hCG). A combination trigger of leuprolide and low-dose hCG was used when ovarian hyperstimulation syndrome risk was felt to be elevated. Trigger was administered when at least 2 lead follicles reached 18 mm in standard cycles and cycles with tamoxifen, while trigger was administered with 2 lead follicles reached 20 mm in letrozole cycles.

Outcomes

The primary cycle outcome of this study was the number of mature oocyte (MII) per antral follicle count (AFC), in order to normalize for baseline ovarian reserve between groups. Additional laboratory outcomes included the total number of oocytes retrieved, total number of MII retrieved, and percentage of patients who were able to cryopreserve greater than ten MII. For patients who underwent more than one cryopreservation cycle, only laboratory outcomes from the first cycle were included.

Statistical analysis

Descriptive statistics (mean, standard deviation [SD], range) were computed by grade and stage for the outcome of our study. The normality of outcome distribution was evaluated using the Shapiro–Wilk test. Student's *t*-test was used to compare the means of outcomes for normally distributed data and the Wilcoxon rank-sum test for non-parametric data. Univariate linear and logistic regression models were performed to assess the association of grade I vs. grade II/III and high vs. low stage with each outcome of interest. Multivariate models that adjusted for factors known to be associated with fertility preservation outcomes, including age, body mass index (BMI), and AFC, were also performed. Results from the univariate and multivariate regression models are presented as unadjusted and adjusted means or percentages by grade and stage. Statistical analyses were performed using Stata Version 15 (Stata Corporation). Two-sided P values < 0.05 were considered significant.

Ethical approval

All study procedures were reviewed and approved by the University of California, San Francisco Committee on Human Research.

Results

Study population

A total of 267 premenopausal patients undergoing breast cancer–related fertility preservation at the University of California, San Francisco Center for Reproductive Health were included in our analysis. All patients underwent a GnRH antagonist protocol for ovarian stimulation. Patients who were missing breast cancer stage or grade information ($N=3$) were excluded from the study.

Of the 267 women, 215 (80.5%) had low-stage disease, while 52 (19.5%) had high-stage disease (Table 1). Women with high-stage disease were younger (33.4 vs. 34.8 years, $P=0.05$) and had higher BMI (25.2 vs. 23.6, $P=0.01$) compared to women with low-stage disease. There were no differences in baseline AFC, total gonadotropin dose, days of stimulation, and follicles ≥ 13 mm on the day of trigger by stage of breast cancer.

With regards to grade, a total of 32 patients (11.9%) had grade I disease, and 235 (88.1%) had grade II/III disease (Table 2). Women with grade I breast cancer tended to be younger than those with grade II/III disease (34.2 vs. 36.6 years, $P=0.01$). BMI, baseline AFC, total gonadotropin dose, days of stimulation, and follicles ≥ 13 on the day of trigger did not differ between the grade cohorts.

Cycle outcomes by breast cancer stage

Cycle outcomes for low-stage and high-stage breast cancer patients are shown in Table 3. After adjusting for age, BMI, and baseline AFC, we found no differences in cycle outcomes by stage of cancer. Specifically, the adjusted mean MII per AFC for low-stage breast cancer patients was 1.0 (95% CI 0.9–1.1), while the mean MII per AFC for high-stage breast cancer patients was 1.1 (95% CI 0.9–1.3) ($P=0.3$). Similarly, when comparing low- and high-stage breast cancer patients, there was no difference in total oocytes retrieved (18.2 vs. 20.0, $P=0.2$), total MII retrieved (12.7 vs. 14.5, $P=0.2$), and percentage of patients who were able to preserve greater than 10 MII (54.3% vs. 61.3%, $P=0.3$).

Table 1 Patient characteristics and cycle outcomes by breast cancer stage

	Low-stage disease ($N=215$)	High-stage disease ($N=52$)	*P* value
Age (years)	34.8 (24–43, SD 4.4)	33.4 (23–44, SD 4.8)	0.05
BMI (kg/m^2)	23.6 (16–40, SD 4.8)	25.2 (17–40, SD 4.9)	**0.01**
AFC (*n*)	14.5 (1–68, SD 9.4)	16.3 (1–55, SD 9.7)	0.15
Total gonadotropin dose (IU)	3780 (270–7650, SD 1134.9)	3685.2 (1350–6750, SD 1023.2)	0.58
Days of stimulation	10.4 (3–26, SD 2.1)	10.0 (7–16, SD 1.9)	0.20
Follicles = > 13 days of trigger (*n*)	14.2 (1–47, SD 8.2)	15.8 (1–29, SD 9.0)	0.20

Legend: *SD*, standard deviation; *BMI*, body mass index; *AFC*, antral follicle count. For all values: Mean (range, standard deviation). Boldface *P* values are statistically significant. Low-stage breast cancer was defined as stages I and II, while high-stage disease was defined as stages III and IV

Table 2 Patient characteristics and cycle outcomes by breast cancer grade

	Grade I disease ($N=32$)	Grade II/III disease ($N=235$)	*P* value
Age (years)	36.6 (27–43, SD 4.7)	34.2 (23–44, SD 4.4)	**0.01**
BMI (kg/m^2)	23.7 (17–40, SD 5.0)	23.9 (16–40, SD 4.8)	0.64
AFC (*n*)	12.6 (1–37, SD 8.1)	15.3 (1–68, SD 9.6)	0.13
Total gonadotropin dose (IU)	3971.1 (2200–7650, SD 1035.4)	3717.6 (270–6750, SD 1122.2)	0.23
Days of stimulation	10.2 (7–16, SD 1.8)	10.3 (2–26, SD 2.1)	0.69
Follicles = > 13 days of trigger (*n*)	12.7 (1–33, SD 8.0)	14.8 (1–47, SD 8.4)	0.17

Legend: *SD*, standard deviation; *BMI*, body mass index; *AFC*, antral follicle count. For all values: Mean (range, standard deviation). Boldface *P* values are statistically significant. Low-grade breast cancer was defined as grade I, while high-grade disease was defined as grades II and III

Table 3 Cycle outcomes by breast cancer stage

	Unadjusted mean (low)	Unadjusted mean (high)	Adjusted mean Age + BMI + AFC (low)	Adjusted mean age + BMI + AFC (high)	Adjusted mean difference (95% CI)	*P* value
Total oocytes retrieved	17.9 (16.2–19.5)	20.7 (17.3–24.0)	18.2 (16.8–19.6)	20.0 (17.0–22.9)	1.78 (−1.5–5.0)	0.3
Total MII retrieved	12.5 (11.3–13.8)	14.8 (12.3–17.4)	12.7 (11.6–13.9)	14.5 (12.2–16.9)	1.80 (−0.8–4.4)	0.2
> 10 MII preserved	53.5% (46.8–50.2%)	63.5% (50.4–76.5%)	54.3% (48.5–60.2%)	61.3% (49.4–73.2%)	6.9% (−6.4 to 20.2%)	0.3
MII/AFC	1.0 (0.9–1.1)	1.1 (0.9–1.3)	1.0 (0.9–1.1)	1.1 (0.9–1.3)	0.15 (−0.1 to 0.4)	0.2

Legend: *SD*, standard deviation; *BMI*, body mass index; *AFC*, antral follicle count

Cycle outcomes by breast cancer grade

Cycle outcomes were also evaluated by breast cancer grade using a multivariate analysis (Table 4). After adjusting for age, BMI, and baseline AFC, we found no difference in MII per AFC (1.0 vs. 1.0, $P = 0.92$), total oocytes retrieved (17.1 vs. 18.9, $P = 0.38$), total MII retrieved (12.3 vs. 13.3, $P = 0.56$), or the percentage of patients who were able to preserve greater than 10 MII (58.9% vs. 55.5%, $P = 0.68$) when comparing those with grade I vs. grade II/III breast cancer. For both breast cancer grade and stage, univariate analyses were also not significantly different between the grade/stage cohorts.

Discussion

Grade and stage of breast cancer malignancy are unlikely to impact the number of mature oocytes retrieved with ovarian stimulation. This analysis suggests that patients with advanced-stage/grade cancers can be counseled that their oocyte yields are not likely to be decreased due to their disease stage/grade.

Plausible biological mechanisms

Prior literature has suggested decreased sperm quality and quantity in men with a diagnosis of cancer, prior to treatment. An epidemiological study of 164 patients showed oligospermia was common prior to initiation of cancer treatment, though sperm parameters of count, motility, and morphology did not differ by cancer type [17]. Other studies have found defective spermatogenesis occurs in a significant portion of Hodgkin's and testicular cancer patients, again, prior to cancer treatment [18, 19]. Furthermore, some studies have also shown a direct association between cancer stage and degree of semen analysis abnormality. It has been hypothesized that this may be secondary to a variety of mechanisms including damage of the germinal epithelium, disruption of the hypothalamic-pituitary–gonadal axis, immunological changes, and variation in body temperature; however, the phenomenon is not well understood currently and other complex factors may also contribute [20].

It has similarly been hypothesized that comparable mechanisms may negatively impact ovarian function and oocyte quality and quantity in women, which may be manifested through a lower number of oocytes retrieved

Table 4 Cycle outcomes by breast cancer grade

	Unadjusted mean (grade I)	Unadjusted mean (grade II/III)	Adjusted mean age + BMI + AFC (low)	Adjusted mean age + BMI + AFC (high)	Adjusted mean difference (95% CI)	*P* value
Total oocytes retrieved	15.3 (11.1–19.6)	19.0 (17.4–20.6)	17.1 (13.5–20.8)	18.9 (17.5–20.2)	1.7 (−2.2–5.6)	0.38
Total MII retrieved	11.1 (7.8–14.4)	13.3 (12.1–14.5)	12.3 (9.4–15.3)	13.3 (12.2–14.3)	0.94 (2.2–4.1)	0.56
> 10 MII preserved	53.1% (35.8–70.4%)	55.9% (49.6–62.2%)	58.9% (44.0–73.7%)	55.5% (49.8–61.1%)	2.8% (−1.5 to 2.1%)	0.68
MII/AFC	1.0 (1.8–1.3)	1.0 (0.9–1.1)	1.0 (0.7–1.2)	1.0 (0.9–1.1)	0.14 (−0.3 to 0.3)	0.92

Legend: *SD*, standard deviation; *BMI*, body mass index; *AFC*, antral follicle count

or mature oocytes cryopreserved in a fertility preservation cycle. However, the process of sperm production is markedly different from that of oocytes, which are not regenerated throughout adult life and may be less sensitive to body temperature changes or other shorter-term metabolic derangements related to developing malignancies. Therefore, there may be significant differences between the effect of cancer on oocytes in comparison to sperm. Prior studies have suggested that features such as generalized inflammatory response and altered systemic vascular function (which may be caused by altered levels of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEG-F)) may also contribute to worsening ovarian function in cancer patients. However, it is unclear if these features vary with the severity of disease [21, 22].

Comparison to prior literature

Prior studies have attempted to evaluate this plausible impact of malignancy on the ovary by evaluating fertility preservation outcomes based on malignancy type and compared to healthy patients undergoing fertility preservation. These data have overall been conflicting; however, our group's 2017 study and 2018 meta-analysis showed cancer diagnosis is not associated with reduced response to ovarian stimulation [13, 23–26]. The meta-analysis included ten case–control retrospective studies with 713 cancer patients and 1,830 healthy controls and found no impact of cancer on mean total oocytes, mature oocytes, 2PNs, and fertilization rates. A subgroup analysis on breast cancer patients only also found no difference in total or mature oocytes between cancer patients and healthy controls. In our prior 2017 article, we found that among 589 patients (191 breast cancer, 398 elective fertility preservation), total and mature oocytes did not differ after adjustment for potential confounders. However, among cancer patients, very few studies have investigated the effect of cancer severity on oocyte cryopreservation outcomes.

Most recently, however, Volodarsky-Perel et al. published a report showing high-grade, as compared to low-grade, cancer was associated with a decreased number of retrieved mature oocytes and cryopreserved embryos [14]. This study, however, was limited by its relatively small sample size and inclusion of several different malignancy types. The analysis included 11 cancer types (with 52 breast cancer patients as the largest cancer type), among 147 total patients. It may be difficult to compare stage and grade across cancers, given the heterogeneity of different cancer types and possible differential effects of grade/stage depending on the cancer type. Another study by the same lead author investigated grade and stage among 155 breast cancer patients and found high-grade tumors were associated with a significantly lower number of mature oocytes than low-grade tumors in pre-treatment fertility preservation cycles, while significant differences were not found between the low- and high-stage groups [15]. However, in both studies, the primary outcome of mature oocytes was not adjusted for ovarian reserve, though baseline AFC counts were similar between study groups and increasing AFC was separately correlated with an increased chance of retrieving > 10 mature oocytes.

With breast cancer being one of the most prevalent cancers of reproductive age women and given the dearth of literature on this subject, we sought to evaluate the impact of cancer grade and stage specifically among a large cohort of breast cancer patients undergoing fertility preservation. Contrary to the prior study, our analysis found that breast cancer grade and stage do not significantly affect the number of oocytes retrieved, number of mature oocytes preserved, and number of mature oocytes per AFC during fertility preservation prior to gonadotoxic therapy (both unadjusted and after adjustment for age, AFC, and BMI). The primary outcome of MII/AFC ranged from 1.0 to 1.1 for our categories of cancer stage and grade, which is within what we would expect clinically if cancer grade/stage was not affecting ovarian stimulation.

There are several possible reasons for discrepant findings between our study and the prior studies by Volodarsky et al. There appeared to be differences in stimulation protocol between the two studies, which may be due to institutional and/or geographical practices; our study was the first to investigate this topic at a single US academic center, while the prior study on breast cancer center was conducted at a single Canadian academic center. Though the patients in our study were older on average compared to those in the prior study, the gonadotropin dose, number of stimulation days, and ultimately the number of oocytes retrieved were higher in our study. Additionally, our study used mixed FSH/hMG protocols while the prior study appeared to use only FSH or hMG. Based on these differences in protocol and retrieval outcomes, this suggests that simulation protocol may impact these oocyte cryopreservation outcomes, and increased gonadotropin doses or mixed gonadotropin protocols may lead to more favorable retrieval outcomes among higher grade breast cancer patients. It is possible that metabolic changes related to breast cancer may change the sensitivity of ovarian follicles to gonadotropins, leading to a differential effect of higher dosing on retrieval outcomes. This is an important area for future study, in terms of possible interaction of stimulation protocol with cancer stage/grade on oocyte cryopreservation outcomes. Additionally, the prior study compared grade I/II with grade III (defined as low and high grade in their cohort), while we compared grade I with grade II/III due to small numbers of grade III cancers in our cohort. Future studies with larger sample sizes should examine each stage separately and make more granular comparisons. Lastly, as our study was retrospective in

nature, we performed a multivariate analysis on the main outcome of the number of MII oocytes/AFC, while the prior studies on the subject cancer grade/stage and fertility preservation did not use multivariate analyses for the primary outcome [14, 15].

Strengths and limitations

The strengths of this study include the large sample size with 267 patients compared to a prior study of 155 breast cancer patients. Our study is also the first study in the USA to investigate cancer grade/stage on fertility preservation outcomes. In addition, our study focused on a homogenous patient population by including breast cancer patients only, as the inclusion of multiple types of cancer in prior studies can make interpretation challenging. We also had detailed information available on patient and cycle characteristics, as all patients were seen at one academic center, which allowed us to control for additional factors which might impact the independent relationship between cancer stage and grade and our outcome of interest.

Study limitations include evaluation of breast cancer patients only though the effect of cancer on stimulation outcomes may differ depending on the type of cancer, as cancers are a heterogenous group of diseases, and therefore, these findings may not be generalizable to other cancer types. This is an important area for future study in terms of investigating this question with larger sample sizes for breast cancer patients. Additionally, while oocytes retrieved and mature oocytes are important clinical metrics, we were not able to follow our cohort to study other important clinical outcomes that indicate oocyte health including embryo quality, embryo euploidy rates, or pregnancy outcomes. Although our study is the largest on this subject to date, the overall sample size is still relatively small, though it is relevant to note that the oncofertility population is small to begin with. We were also not able to study other characteristics of breast cancer including tumor size and hormone status, for possible effects on our outcomes of interest, given relatively small sample sizes. These are important areas of future study in larger cohorts.

Conclusions

In a relatively large cohort of breast cancer patients, we found stage and grade of breast cancer do not affect clinical outcomes of oocytes retrieved and mature oocytes cryopreserved (after adjustment for AFC). This is important information that can be used to counsel breast cancer patients who are undergoing fertility preservation prior to gonadotoxic therapy. We suspect the independent effect of cancer on ovarian stimulation may vary depending on the type of malignancy and highlights the need for further evaluation within populations of specific cancer types. Additionally, important areas for future investigation include longer-term outcomes on embryo quality, pregnancy data, and cancer treatment outcomes by pre-treatment cancer grade and stage.

Acknowledgements We would like to make a special thanks to our nurses and care coordinators who provided patient education and fertility preservation coordination.

Author contribution K.W, A.W., M.K.A., and J.R.M.'s roles included data collection, data analysis, and manuscript writing; J.M.L.'s roles included study design and data collection; E.M.L., M.I.C., and M.R.'s roles included study design and manuscript writing. All author roles meet the following criteria: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was supported by departmental research funding within the University of California, San Francisco Department of Obstetrics, Gynecology, and Reproductive Sciences.

Data availability We are unable to provide our data due to its identified nature.

Code Availability Code may be made available upon request.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of California, San Francisco (UCSF) Committee on Human Research and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication As part of the consent process, all participants gave written consent to use de-identified information for research purposes and publications.

Conflict of interest The authors declare no competing interests.

References

1. Society. AC. Breast Cancer Facts & Figures 2019–2020. In: Society AC, ed., 2019.
2. Ethics Committee of the American Society for Reproductive Medicine. Electronic address Aao. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril. 2018;110:380–65.
3. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994–2001.

4. Anazodo A, Ataman-Millhouse L, Jayasinghe Y, Woodruff TK. Oncofertility-an emerging discipline rather than a special consideration. Pediatr Blood Cancer. 2018;65:e27297.
5. Letourneau JM, Sinha N, Wald K, Harris E, Quinn M, Imbar T, et al. Random start ovarian stimulation for fertility preservation appears unlikely to delay initiation of neoadjuvant chemotherapy for breast cancer. Hum Reprod. 2017;32:2123–9.
6. Letourneau JM, Wald K, Sinha N, Juarez-Hernandez F, Harris E, Cedars MI, et al. Fertility preservation before breast cancer treatment appears unlikely to affect disease-free survival at a median follow-up of 43 months after fertility-preservation consultation. Cancer. 2020;126:487–95.
7. Moravek MB, Confino R, Smith KN, Kazer RR, Klock SC, Lawson AK, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril. 2018;109:349–55.
8. Baker JA, Buck GM, Vena JE, Moysich KB. Fertility patterns prior to testicular cancer diagnosis. Cancer Causes Control. 2005;16:295–9.
9. Hendry WF, Stedronska J, Jones CR, Blackmore CA, Barrett A, Peckham MJ. Semen analysis in testicular cancer and Hodgkin's disease: pre- and post-treatment findings and implications for cryopreservation. Br J Urol. 1983;55:769–73.
10. Spermon JR, Ramos L, Wetzels AM, Sweep CG, Braat DD, Kiemeney LA, et al. Sperm integrity pre- and post-chemotherapy in men with testicular germ cell cancer. Hum Reprod. 2006;21:1781–6.
11. Viviani S, Ragni G, Santoro A, Perotti L, Caccamo E, Negretti E, et al. Testicular dysfunction in Hodgkin's disease before and after treatment. Eur J Cancer. 1991;27:1389–92.
12. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effects of Hodgkin's disease and combination chemotherapy on gonadal function in the adult male. Cancer. 1982;49:418–22.
13. Turan V, Quinn MM, Dayioglu N, Rosen MP, Oktay K. The impact of malignancy on response to ovarian stimulation for fertility preservation: a meta-analysis. Fertil Steril. 2018;110:1347–55.
14. Volodarsky-Perel A, Cohen Y, Arab S, Son WY, Suarthana E, Dahan MH, et al. Effects of cancer stage and grade on fertility preservation outcome and ovarian stimulation response. Hum Reprod. 2019;34:530–8.
15. Volodarsky-Perel A, Cai E, Tulandi T, Son WY, Suarthana E, Buckett W. Influence of stage and grade of breast cancer on fertility preservation outcome in reproductive-aged women. Reprod Biomed Online. 2020;40:215–22.
16. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 2002;41:154–61.
17. Chung K, Irani J, Knee G, Efymow B, Blasco L, Patrizio P. Sperm cryopreservation for male patients with cancer: an epidemiological analysis at the University of Pennsylvania. Eur J Obstet Gynecol Reprod Biol. 2004;113(Suppl 1):S7-11.
18. Tal R, Botchan A, Hauser R, Yogev L, Paz G, Yavetz H. Follow-up of sperm concentration and motility in patients with lymphoma. Hum Reprod. 2000;15:1985–8.
19. Padron OF, Sharma RK, Thomas AJ Jr, Agarwal A. Effects of cancer on spermatozoa quality after cryopreservation: a 12-year experience. Fertil Steril. 1997;67:326–31.
20. Rueffer U, Breuer K, Josting A, Lathan B, Sieber M, Manzke O, et al. Male gonadal dysfunction in patients with Hodgkin's disease prior to treatment. Ann Oncol. 2001;12:1307–11.
21. Rubin H. Systemic effects of cancer: role of multiple proteases and their toxic peptide products. Med Sci Monit. 2005;11:RA221-8.
22. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
23. Almog B, Azem F, Gordon D, Pauzner D, Amit A, Barkan G, et al. Effects of cancer on ovarian response in controlled ovarian stimulation for fertility preservation. Fertil Steril. 2012;98:957–60.
24. Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. Hum Reprod. 2018;33:2051–9.
25. Das M, Shehata F, Moria A, Holzer H, Son WY, Tulandi T. Ovarian reserve, response to gonadotropins, and oocyte maturity in women with malignancy. Fertil Steril. 2011;96:122–5.
26. Quinn MM, Cakmak H, Letourneau JM, Cedars MI, Rosen MP. Response to ovarian stimulation is not impacted by a breast cancer diagnosis. Hum Reprod. 2017;32:568–74.