A predictive model for chemotherapy-related diminished ovarian reserve in reproductive-age women

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Objective: To develop and internally validate a clinical predictive tool to assess the likelihood that a young cancer patient will experience diminished ovarian reserve (DOR) after chemotherapy.
Design: Prospective cohort study.
Setting: University hospitals.
Patient(s): Postpubertal adolescent and young adult women with a new diagnosis of cancer requiring chemotherapy.
Intervention: None.
Main Outcome Measure(s): Diminished ovarian reserve after completion of and recovery from chemotherapy, defined as serum antimüllerian hormone (AMH) <1 ng/mL at 8–24 months after completion of chemotherapy.
Result(s): A multivariable logistic regression model which includes age, cancer type, exposure to an alkylating agent, and baseline AMH value accurately predicts the diagnosis of DOR after chemotherapy with an area under the receiver operating characteristic curve of 0.89.
Conclusion(s): Pretreatment information on age, cancer type, use of an alkylating agent, and baseline AMH levels make up a clinically useful predictive tool to identify which women are most at risk for DOR caused by chemotherapy. (Fertil Steril® 2021;115:431–7. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: AMH, ovarian reserve, fertility preservation, chemotherapy

Thousands of reproductive-age women are diagnosed with cancer every year. Advancements in cancer therapies have improved survival, but many of the treatments have been associated with infertility and early menopause (1, 2). Before undergoing chemotherapy, young cancer patients require counseling regarding their future reproductive potential and options for fertility preservation including mature oocyte cryopreservation, embryo cryopreservation, and ovarian tissue freezing before chemotherapy. At this time, physicians cannot easily predict which patients are most at risk for chemotherapy-related diminished ovarian reserve (DOR), nor can they identify women who are at very low risk and would be unnecessarily subjected to side-effects from time-intensive and costly procedures.

The number of oocytes that exist in the ovary before chemotherapy is known as the baseline ovarian reserve. Although there is no way to count an individual's oocytes in vivo, several biochemical markers and ultrasound measurements, including serum antimüllerian hormone (AMH) and ultrasound antral follicle count (AFC), have been established as proxy markers of ovarian reserve. Chemotherapeutic agents are known to cause infertility by depleting the existing ovarian follicle pool, and the extent of damage to the follicles depends on the specific chemotherapeutic agent, age at exposure, and

Received April 10, 2020; revised July 31, 2020; accepted August 5, 2020; published online January 15, 2021.
M.M.H. reports National Institutes of Health (NIH) T32 Training Grant HD007440 during the conduct of the study. K.E.C. has nothing to disclose. M.P. has nothing to disclose. K.B. has nothing to disclose. J.P.G. has nothing to disclose. M.D.S. has nothing to disclose. C.R.G. reports NIH grant RO1-HD062797-01 during the conduct of the study. The NIH did not play any role in study design, in the analysis or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.
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Fertility and Sterility® Vol. 115, No. 2, February 2021 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2020.08.003

dosage (3, 4). However, there are very few studies that have prospectively assessed ovarian reserve before chemotherapy and again at time points after completion of initial cancer treatment to determine which individuals are at highest risk of ovarian insufficiency after treatment. In addition, such studies have primarily been conducted in breast cancer patients with ages ranging to the late thirties or even early forties and cannot be extrapolated to younger populations with different diagnoses and treatments (5, 6).

The ability to predict whether a young cancer patient's ovarian reserve will withstand the required cancer treatment would vastly improve our ability to counsel patients regarding their future reproductive potential and to know who will benefit from fertility-preservation therapies (7, 8). The primary objective of the present study was to develop and internally validate a clinical predictive tool to assess the likelihood that a young cancer patient will experience DOR after chemotherapy. This model could be used before initiation of chemotherapy to guide recommendations regarding the need to pursue fertility-sparing therapies. We hypothesized that ovarian reserve measured at baseline and exposure to chemotherapy with an alkylating agent may predict DOR at 8–24 months after end of treatment.

MATERIALS AND METHODS

This was a multicenter prospective cohort study conducted at five medical centers in the United States: University of Pennsylvania (Penn), Children's Memorial Hospital (CMH), Children's Hospital of Philadelphia (CHOP), University of North Carolina (UNC), and University of California, San Diego (UCSD). Data were collected from 2007 to February 2016. Patients were enrolled in a longitudinal cohort study called Ovarian Reserve After Cancer: Longitudinal Effects (ORACLE). Young women with newly diagnosed cancer were referred to a reproductive endocrinologist for consultation regarding fertility preservation options. They were enrolled in ORACLE before the onset of cancer therapy. Inclusion criteria at enrollment were postmenarchal women of age 11–45 years, with the presence of a uterus and at least one ovary, and anticipating chemotherapy. Approval of the study was obtained from the University of Pennsylvania's Institutional Review Board (protocol no. 809406) (9).

Participants were excluded if they were pregnant at enrollment, if they reported lactation within the previous month, if they had any history of previous treatment with chemotherapy or radiation with the exception of radioactive iodine for thyroid cancer, if they carried a previous diagnosis of an illness associated with premature ovarian failure (Turner syndrome, fragile X permutation carrier), or if they had any endocrine disorder associated with irregular menstrual cycles (Cushing disease, thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia, polycystic ovary syndrome). As part of the ORACLE study, participants were asked to complete study visits every 3 months after the initiation of chemotherapy. Study visits included questionnaires, blood drawing for hormonal analysis (AMH, FSH, E_2), and a pelvic ultrasound with the measurement of AFC. For the purpose of this analysis, participants were excluded if they did not have at least one pretreatment visit with serum collection and at least one follow-up visit (with serum collection) 8–24 months after chemotherapy.

Primary Outcome

The primary outcome was DOR (defined as an AMH level <1 ng/mL on a Gen2 assay) at 8 to 24 months from the completion of cancer treatment. AMH is secreted by the granulosa cells of the ovaries and is a surrogate measure that reflects the remaining existing follicle pool in the ovaries. AMH has been shown to histologically correlate with the remaining follicle pool (10), is potentially a predictor of time to menopause (11), and is currently regarded as the best quantitative estimate of ovarian reserve. In the infertile population, AMH <1 ng/mL is associated with poor outcomes after infertility treatment, and this has been well validated (12–14). Clinically, it is important to identify those patients at high risk for having AMH <1 ng/mL after chemotherapy treatment to identify those most in need of cryopreservation of oocytes or embryos.

Eight to 24 months was chosen as the optimal time to reassess the AMH level, because ovarian reserve can recover somewhat after cancer treatment, but it may require 6 months to 1 year. If measured too soon after chemotherapy, serum AMH could underestimate the patient's true ovarian reserve (9).

Correlation of AMH Assays

It is important to recognize that AMH assays have evolved over the past 25 years and there are currently several assays available. The Beckman Coulter Gen II is currently the most commonly used clinical assay and was the most common in published literature until 2012. Thereafter, AnshLabs introduced two new AMH assays. For this study, after collection, serum was aliquotted and stored at -80°C. Samples were originally tested with the use of Beckman Coulter Gen II assay, and later the Ansh picoAMH owing to its superior sensitivity at the lower limits of detection. In some cases, there was insufficient serum to test the samples with both assays. The correlation of the picoAMH compared with the Gen II assay has previously been published as 1:1.77 (15). We validated this conversion within our own data and found the same correlation (Supplemental Fig. 2, available online at www.fertstert.org). To be comparable to the existing literature, we converted serum values that were run only on the picoAMH assay to the Gen II assay scale.

For the purpose of this study, chemotherapy-related DOR is defined as AMH <1 ng/mL on the Gen II assay or $<1{,}770$ pg/mL on the picoAMH assay at 8–24 months after chemotherapy. Those values that were measured with the picoAMH were converted based on the formula above.

Candidate Predictor Variables

The following variables were hypothesized to be predictors of chemotherapy-related DOR: baseline measures of ovarian reserve (AMH, FSH, E_2, AFC), age, exposure to an alkylating agent at any dose, and cancer type. Serum blood samples

were obtained in the early follicular phase if possible for determining levels of FSH, E_2, and AMH. AFC was measured by transvaginal ultrasound during the early phase of the menstrual cycle (days 2–5) for regularly menstruating participants and randomly for irregular or amenorrheic participants. AFC was determined as the number of follicles 2–10 mm in average diameter for subjects undergoing transvaginal ultrasonography when both ovaries were visualized. In some cases, a baseline transvaginal ultrasound was unable to be obtained owing to patient discomfort, adolescent age, or urgent need for chemotherapy. Exposure to an alkylating agent was categorized as yes or no. Although this exposure occurs during treatment, it would be known before the beginning of treatment and can therefore be used in a predictive model. Cancer type was categorized as breast cancer, lymphoma, and "other." The "other" cancer type category included participants with leukemia and ovarian/germ cell, cervical, gastrointestinal, renal, bone, and lung cancers. Statistical analyses were performed with the use of STATA software version 14.1.

Sample size. A priori the sample size was set at 105 for feasibility. With 105 eligible participants, there would be 80% power to detect a relative risk of 1.7, that is, 80% power to detect 85% prevalence of AMH <1 ng/mL among those women with an alkylator score >2 compared with 50% prevalence of AMH <1 ng/mL among all others. This calculation assumes an alpha of 0.05, and assumes 20% prevalence of a total alkylator score >2. The alkylator agent dose score has been used extensively in research studies to quantify alkylating agent exposure (16, 17).

Statistical modeling techniques. Univariate logistic regression was performed with an alpha criterion of ≤ 0.2 to identify which prespecified predictor variables were associated with the primary outcome. Multivariate logistic regression modeling was then used to examine the adjusted association of each predictor variable with the outcome. To yield a reduced-form model that would be more practical for clinical use, backward step-down variable selection techniques with an alpha criterion of ≤ 0.05 was used to decide which variables were independent predictors.

Additional variables of interest. Many women, especially breast cancer patients, require hormones such as leuprolide or tamoxifen after chemotherapy. A priori, we identified that these variables may confound hormone measures. Because they happen after the initiation of chemotherapy, these posttreatment variables cannot be accounted for in a predictive model (that should only include variables that are measurable before chemotherapy). A sensitivity analysis was performed, removing these potential confounding variables to assess their effects on the predictive ability of the model. Hormonal contraceptives, obesity, and smoking may also confound AMH measures, and additional restricted sensitivity analyses were performed to assess the effect of these variables on the final prediction model.

Assessment for age-baseline AMH interaction. A priori, we hypothesized that age may be an effect modifier of baseline AMH, such that AMH may decrease faster after compared with before the age of 30 years (18). An interaction between age and baseline AMH was assessed during the final model building.

Model performance. We use the C-statistic or area under the receiver operating characteristic curve (AUC) to assess the ability of the models to discriminate between high- and low-risk individuals. The AUC measures the probability of concordance between pairs of predicted and actual outcomes, that is, model-predicted high risk for DOR and an observed outcome of DOR.

Bootstrap internal validation. Internal validation of the final prediction model was assessed with the use of 800 bootstrap replications with replacement. Bootstrapping randomly resamples with replacement from the dataset to develop a 95% confidence interval (CI) for the AUC. This type of internal validation estimates the likely future performance of the model on new patients of the same types.

RESULTS

A total of 176 participants with cancer had been enrolled into the ORACLE longitudinal study. A total of 102 participants had completed cancer therapy and were able to be recruited for at least one follow-up visit that occurred 8–24 months after completion of chemotherapy. Seventy-seven eligible participants were recruited from Penn, 9 from CMH, 10 from CHOP, 3 from UNC, and 3 from UCSD.

The baseline characteristics of the 102 participants are presented in Table 1. The mean age was 27 years (range

TABLE 1

Characteristics of participants and prespecified candidate predictor variables.

Characteristic	Total cohort (n = 102)
Age at baseline, y	28.3 (23.1-32.5)
Age at 1 y after end of chemotherapy, y	29.7 (24.7-34.7)
Past pregnancy	22 (21.6%)
BMI, kg/m^2, mean (range)	24.3 (14.8-41.8)
Race	
African American or Black	7 (6.9%)
Caucasian or White	85 (83.3%)
Other	10 (9.8%)
Smoking at study enrollment	3 (2.9%)
Cancer type	
Breast	39 (38.2%)
Lymphoma	34 (33.3%)
Leukemia	8 (7.8%)
Sarcoma	8 (7.8%)
Other	13 (12.7%)
Regular menses at study enrollment	93 (91.2%)
Hormonal contraceptive use at study enrollment	15 (14.7%)
Baseline AMH by cancer type, ng/mL	
Breast	1.8 (1.0-3.0)
Lymphoma	1.4 (0.8-2.2)
Leukemia	1.7 (0.5-2.7)
Sarcoma	1.7 (1.0-2.7)
Other	1.1 (0.4-1.6)

Note: Unless specified otherwise, values are presented as median (interquartile range) or n (%).

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13.5–41.7), median age was 28.3 years (interquartile range [IQR] 23–32). Most participants were normal weight (mean body mass index [BMI] of 24.3 kg/m^2) and white (83%). There were very few smokers (3%). 21.6% (22/102) had a pregnancy before their diagnosis of cancer. Ninety-one percent reported regular menses at enrollment. Fifteen percent (15/102) were on hormonal contraception at the initial enrollment visit. The cohort was heterogeneous in terms of cancer diagnosis, consisting of breast cancer (38.2%), lymphoma (33.3%), leukemia (7.8%), sarcoma (7.8%), and other cancer types (12.7%). Sixty-three percent received an alkylating agent as part of their chemotherapy regimen, 8.8% received radiation to the pelvis, and 17.7% received hormonal therapy as part of their cancer treatment (11.8% tamoxifen, 5.9% leuprolide). Median ovarian reserve parameters at baseline before chemotherapy were consistent with normative data from healthy populations: median AMH was 2.5 ng/mL (IQR 1.4–4.4), median FSH was 6.14 ng/mL (IQR 3.7–7.7), and median AFC was 20 (IQR 11–30).

Eighty-one participants (79.4%) had an AMH <1 ng/mL at 8–24 months after completion of chemotherapy and were considered to have DOR. Univariate analysis of baseline covariates revealed that higher baseline AMH and AFC were protective against DOR. Patients with lymphoma and other cancer types had a lower risk of DOR than patients with breast cancer. Those who were exposed to alkylating agents had a highly increased risk of DOR (Supplemental Table 1, available online at www.fertstert.org). Baseline AMH, baseline AFC, cancer type, and alkylating agent use were associated with the outcome of DOR with a *P* value of <.2 and were tested for the final model building. BMI and day 3 FSH were not associated with DOR. Although it was not associated with DOR in the unadjusted analysis, age at diagnosis was tested in the multivariate model because age is a well known predictor of DOR in the literature.

Multivariate logistic regression modeling was used to estimate the adjusted odds ratios (ORs) for each predictor (Table 2). Age, cancer type, baseline AMH, and exposure to an alkylating agent were retained in the final model, because they were statistically significant or they improved the model's ability to predict the outcome. To simplify the model for clinical use, age was transformed from a continuous to a dichotomous variable, pretreatment age <30 or ≥30 years, and results remained robust. During final model building, age was tested as an effect modifier of baseline AMH, and the interaction term was not significant (*P*=.4), indicating that the rate of change of AMH was not different in those age <30 years and those age ≥30 years. Sensitivity analysis was performed varying the outcome as DOR defined by AMH <0.7 ng/mL, and results remained robust.

Final model performance was assessed by the AUC, which was 0.89 (Fig. 1). Internal validation of the final predictive model was assessed by means of bootstrapping with replacement to develop a 95% CI for the AUC: 0.83–0.95.

In a restricted analysis excluding participants who were taking treatment-related hormones (tamoxifen or leuprolide) after chemotherapy, the AUC was 0.92 (95% CI 0.86–0.98). After bootstrapping, the CI for this curve overlaps with that of the unrestricted analysis and therefore was not significantly different. A similar restricted analysis was performed removing patients who had radiation to the pelvis (n = 9), and neither the ORs in the model nor the AUC was significantly affected.

TABLE 2

Predictive model of chemotherapy-related diminished ovarian reserve.

Variable	OR	*P* value	95% CI
Age, y			
<30	Reference	–	–
≥30	4.4	.074	0.9–22.7
Cancer			
Breast	Reference	–	–
Lymphoma	0.2	.09	0.03–1.2
Other	4.4	.19	0.5–40
Baseline AMH (continuous)	0.51	.005	0.3–0.8
Exposure to alkylating agent (yes or no)	10.3	.002	2.3–45.4

CI = confidence interval; OR = odds ratio.

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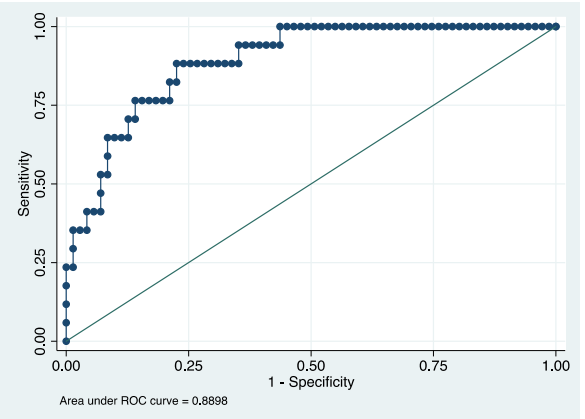
DISCUSSION

Women of reproductive age who will be undergoing chemotherapy are at risk for reduced fertility. All young women facing cancer treatment should be informed of the risks of treatment to their future reproductive potential and the options for preserving fertility, including oocyte and embryo cryopreservation (2). However, these methods can be costly and invasive, have the potential to delay cancer treatment, and do not guarantee a future pregnancy. A decision about whether or not to pursue fertility-preserving therapies must often be made quickly, during a life crisis: the time of a new cancer diagnosis. Because this can be a chaotic time, patients require more precise information regarding their future

FIGURE 1



Receiver operating characteristic (ROC) curve assessing performance of predictive model of chemotherapy-related diminished ovarian reserve: area under the curve = 0.89 (95% CI 0.83–0.95).

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reproductive potential and direct guidance to support their decision making about fertility preservation while anticipating chemotherapy (7). Within the short window of time before chemotherapy, the patient must have the opportunity to understand her individual risk of gonadal failure with a specific proposed cancer treatment. Age, cancer type, exposure to an alkylating agent, and baseline AMH can accurately predict which women are most at risk for DOR caused by chemotherapy. Although these factors have been identified retrospectively as risk factors for subsequent ovarian failure, this study has used prospectively collected data to develop a tool to predict the risk of DOR after chemotherapy for individuals. This novel predictive model provides a metric to be used when counseling patients about their specific need for fertility preservation therapies before chemotherapy.

Within this model, the two most influential predictors of chemotherapy-related DOR are baseline ovarian reserve, and exposure to an alkylating agent. A higher baseline AMH was protective against DOR: OR 0.51, 95% CI 0.3–0.8, $P=.005$. These results are consistent with previous studies that showed pretreatment AMH to be predictive of both long-term ovarian function and time to return of menses in breast cancer patients (5, 19). In this study population, exposure to an alkylating agent caused a tenfold increased risk of DOR: OR 10.3, 95% CI 2.3–45.4, $P=.002$. This confirms previous reports in the literature demonstrating that alkylating agents have the highest potential to cause chemotherapy-related ovarian failure (3, 20).

There are very few studies that have assessed ovarian reserve before chemotherapy and again at time points after completion of initial cancer treatment. Most of those studies have been in cohorts of breast cancer patients. One study developed a prognostic score to estimate time to ovarian recovery after chemotherapy among patients with breast cancer 23-45 years of age, with a median age of 39 years (5). Anderson et al. found markers of ovarian reserve before chemotherapy to be predictors of post-chemotherapy amenorrhea. However, that older patient population, with a mean age of 42.6 years old, cannot be generalized to younger women (6). The present study is unique in developing a predictive tool in a young cohort of patients with heterogeneous cancer types and is more representative of the population presenting for discussion of fertility preservation.

This study has several limitations. First, there is potential for selection bias regarding which patients are referred, or choose to present, to a reproductive endocrinologist to discuss fertility preservation before chemotherapy. It is possible that patients who are too ill to delay treatment will not be referred for discussion, or that oncologists did not refer patients for whom they deemed the risk to be low. Validation in an external cohort is needed to confirm the tool's utility in other populations. Second, this is a heterogeneous population in terms of cancer and treatment types, although it is representative of women presenting for fertility preservation counseling. This heterogeneity was accounted for by including type of cancer as a variable in the model, as well as by using exposure to an alkylating agent as one of the main predictors. However, there may be subtle differences that occur among more rare cancer types that may not be accounted for with this small sample size. For example, our study population included only nine participants exposed to pelvic radiation. Although our analysis did not show pelvic radiation as a significant predictor, nine is not a robust enough sample size to be informative and this model should not be used for patients planning pelvic radiation.

Because AMH is a surrogate marker for fertility, results must be interpreted with caution. This is not a clinical predictive tool for future pregnancy, and it is important to note that AMH has limited predictive value for fertility in a population of women who have not yet attempted conception (21). Ideally, a predictive tool could eventually be developed within a longitudinal population of cancer patients who were treated, attempted pregnancy, and delivered a live-born baby. Because there are many additional factors (behavioral, socioeconomic, medical, and temporal) that affect whether a young cancer patient will ever attempt conception and have a future pregnancy, pregnancy after chemotherapy was not a feasible outcome for this study. We believe that AMH is an important outcome because it has been validated in the infertility population (12) and validated as a marker of the remaining follicle pool (10). AMH is currently the best quantitative measure of gonadotoxicity after chemotherapy.

Clinically, a pre-chemotherapy serum AMH value is a practical assessment, because it is an available assay in most hospitals and the level is stable across the menstrual cycle (22). AMH determined at the time of cancer diagnosis, combined with knowledge of the patient's age, cancer type, and proposed chemotherapy can provide a patient-specific quantitative risk of DOR to aid the oncologist, reproductive endocrinologist, and patient in the decision of whether to pursue oocyte, embryo, or ovarian tissue banking before chemotherapy. For example, according to our model, a 26-year-old with lymphoma and baseline AMH of 6 ng/mL who will not receive an alkylating agent for chemotherapy has only a 5% chance of DOR after chemotherapy. This patient may forego fertility preservation, based on this information. On the other hand, a 28-year-old with breast cancer and baseline AMH of 6 ng/mL who will receive an alkylating agent has a 65% chance of DOR and therefore would be more likely to decide to pursue fertility preservation methods. Future studies are needed to externally validate the model in a new cohort of patients, test the utilization of the tool among reproductive endocrinologists and oncologists, and test how the tool affects patient decision making regarding use of fertility-sparing therapies.

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Un modelo predictivo para reserva ovárica disminuida relacionada con la quimioterapia en mujeres en edad reproductiva.

Objetivo: Desarrollar y validar internamente una herramienta de predicción clínica para evaluar la probabilidad de que un paciente joven con cáncer experimente reserva ovárica disminuida (DOR) después de la quimioterapia.

Diseño: Estudio de cohorte prospectivo.

Entorno: Hospitales universitarios.

Paciente(s): Adolescentes pospúberes y mujeres adultas jóvenes con un nuevo diagnóstico de cáncer que requiere quimioterapia.

Intervención: ninguna.

Principales medidas de resultado: Reserva ovárica disminuida después de la finalización de la quimioterapia y la recuperación de la misma, definida como hormona anti-Mülleriana (AMH) <1 ng / mL a los 8-24 meses después de completar la quimioterapia.

Resultado (s): Un modelo de regresión logística multivariable que incluye la edad, el tipo de cáncer, la exposición a un agente alquilante y el valor basal de AMH predice con precisión el diagnóstico de DOR después de la quimioterapia con un área debajo de la curva característica operativa del receptor (ROC) de 0,89.

Conclusión (es): La información previa al tratamiento sobre la edad, el tipo de cáncer, el uso de un agente alquilante y los niveles basales de AMH constituyen un herramienta predictiva útil para identificar qué mujeres están en mayor riesgo de DOR causado por la quimioterapia.