ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Impact of cancer treatment on risk of infertility and diminished ovarian reserve in women with polycystic ovary syndrome

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Objective: To compare markers of fertility and ovarian reserve between cancer survivors and cancer-free women with and without polycystic ovary syndrome (PCOS).
Design: Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study—a population-based cohort study.
Setting: Not applicable.
Patient(s): Female cancer survivors (n = 1,090) aged 22–45 years, diagnosed between ages 20 and 35 years, and at least 2 years after diagnosis; 369 participated in a clinic visit. Three hundred seventy-four reproductive-aged women without cancer also completed a clinic visit.
Intervention(s): None.
Main Outcome Measure(s): Infertility, time to first pregnancy after cancer diagnosis, and measures of ovarian reserve (antimüllerian hormone [AMH] and antral follicle count [AFC]).
Results: Seventy-eight cancer survivors (7.2%) reported a PCOS diagnosis, with 41 receiving gonadotoxic treatment. Survivors with PCOS exposed to gonadotoxic treatment (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.2–4.5) and unexposed (OR 3.4, 95% CI 1.7–6.9) were more likely to report infertility than unexposed survivors without PCOS and were more likely to have fewer children than desired (exposed: OR 2.1, 95% CI 1.0–4.2; unexposed: OR 3.0, 95% CI 1.4–6.8). After adjusting for age, comparison women with PCOS had the highest markers of ovarian reserve (AMH: 2.43 ng/mL, 95% CI 1.22–4.82 ng/mL; AFC: 20.7, 95% CI 15.3–27.8), and cancer survivors without PCOS treated with gonadotoxic agents had the lowest levels (AMH: 0.19 ng/mL, 95% CI 0.14–0.26 ng/mL; AFC: 7.4, 95% CI 6.4–8.5).
Conclusion(s): Despite having higher AMH and AFC on average after cancer treatment, cancer survivors with PCOS were less likely to meet their reproductive goals compared with survivors without PCOS. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Cancer, infertility, ovarian reserve, polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) affects approximately 5%–10% of women, making it the most common endocrine abnormality in women of reproductive age (1, 2). Characterized by oligo-ovulation or anovulation, clinical or biological evidence of hyperandrogenism, and polycystic ovaries on ultrasound (3), PCOS is one

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of the most common causes of female infertility (4). Recent work in the field of oncofertility (5) has shown that some cancer treatments can diminish or deplete ovarian reserve in multiple different types of cancers (6–9). However, there is little information about fertility and ovarian reserve in women with PCOS who had cancer during their reproductive years.

Women diagnosed with PCOS who undergo treatment for cancer may have different reproductive outcomes than women without PCOS. Polycystic ovary syndrome is associated with higher anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) as assessed by transvaginal ultrasound (10–13). Because AMH and AFC are correlated with the primordial follicle pool, these markers provide an estimate for ovarian reserve (14). Cancer treatment, especially gonadotoxic chemotherapy and radiation, is known to decrease a woman's ovarian reserve. However, it is unclear whether women with PCOS may be somewhat protected from gonadotoxic therapy because they have a higher ovarian reserve before treatment, and if so, how this impacts their risk for infertility. Given that women with PCOS are already at a higher risk of infertility compared with those without PCOS, it is important to determine how a coexisting cancer diagnosis may affect this high-risk group. The primary objective of this study was to compare markers of fertility and ovarian reserve between cancer survivors with and without PCOS. Secondarily, cancer survivors were compared with women with and without PCOS who have no history of cancer.

MATERIALS AND METHODS

Study Population

We used data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study. The FUCHSIA Women's Study is a population-based study examining the effect of cancer treatment during the reproductive years on future fertility. Eligibility criteria included the following: female; diagnosed with a reportable malignant cancer (15) or ductal carcinoma in situ between the ages of 20 and 35 years; diagnosed between 1990 and 2009; aged 22–45 years at the time of enrollment in the study between 2012 and 2013; and at least 2 years since cancer diagnosis at enrollment. Eligible cancer survivors were identified in collaboration with the Georgia Cancer Registry (GCR). A total of 1,282 cancer survivors completed the telephone interview. Women were excluded from this analysis if they had a hysterectomy or bilateral oophorectomy before their cancer diagnosis or as part of their initial cancer treatment, because they would not be able to become pregnant after cancer treatment. Women with a uterus and at least one ovary were invited to participate in a substudy to assess clinical markers of fertility; 369 cancer survivors completed a clinic visit.

Comparison women with no history of cancer were invited to participate in the telephone interview to represent the general population. Comparison women were told that the study would compare the health of women who survived cancer with the health of women who did not have cancer. Women were recruited using a commercial list that was frequency-matched to the cancer survivors according to age and location of residence in the state of Georgia. Comparison women were eligible to participate if they were aged 22–45 years at the time of recruitment. Eligible comparison women were also invited to participate in the substudy to measure markers of ovarian reserve; 376 comparison women came to the clinic.

The institutional review boards of Emory University and the Georgia Department of Public Health approved this study.

Procedures

All study participants completed a detailed telephone interview about their reproductive histories, including questions regarding demographic characteristics, pregnancy history, medical conditions, lifestyle factors, periods of infertility, and reproductive goals. Cancer survivors were asked about cancer diagnosis and treatments received. During the interview, women were asked whether they had ever been diagnosed with PCOS; if they responded yes, they were then asked whether a doctor diagnosed their PCOS, the age at which it was diagnosed, and what signs or symptoms they experienced. Women who did not answer the question about a history of PCOS (survivor: n = 13; comparison: n = 2) were excluded. We asked women whether they had a period of time during which they had regular (at least three times per month) unprotected sex with a male partner for 6 months or longer but did not get pregnant. Those who responded in the affirmative were asked for the age at which this subfertile period occurred, the length of time for which it continued, whether they were actively trying to get pregnant during this time, and whether they got pregnant at the end of this period. Further, for each pregnancy that a woman reported, she was asked how long she was having regular unprotected sex before the pregnancy. Whether a woman had met her reproductive goals was calculated by subtracting the number of children a woman had given birth to from the reported number of children the woman desired.

Information regarding cancer diagnosis, cancer type, and treatment for cancer survivors, including exposure to gonadotoxic treatment, was abstracted from medical records and the GCR and compared with self-reported exposures. Gonadotoxic treatment was defined as receipt of systemic chemotherapy, total body irradiation, or radiation to the abdomen or pelvis. Participants who had evidence of administered chemotherapy in their medical records or who did not have records available but reported chemotherapy exposure that was confirmed by the GCR were considered exposed to gonadotoxic chemotherapy treatment. Those who had total body irradiation or radiation to the abdomen or pelvis documented in their medical record or who did not have records available but self-reported radiation and the GCR indicated radiation for cervical, ovarian, colon, endometrial, kidney, placental, or vaginal cancer were considered exposed to gonadotoxic radiation treatment.

Clinic visits took place at participating reproductive clinics across the state of Georgia. Clinic visits included a blood draw and a transvaginal ultrasound. A trained sonographer performed transvaginal ultrasound scans and