Beyond decreased ovarian reserve: considering reproductive comorbidities in female cancer survivors

In the United States, there are >400,000 female cancer survivors of reproductive age (between 15 and 45 years old), many of whom had not met their reproductive goals when they were diagnosed with cancer (1). The field of oncofertility emerged from an unmet need to address reproductive late effects of cancer treatments, namely infertility, following strides in improving long-term survival in this population. At present, a girl or young woman who is diagnosed with cancer can expect to have >80% chance of surviving >5 years. Because of observations that radiation involving ovaries and some systemic chemotherapy increase ovarian failure and infertility clinically and decrease the number of ovarian follicles histologically, fertility risk counseling has primarily focused on decreased ovarian reserve and offering fertility preservation by oocyte or ovarian tissue banking before cancer treatments. The novelty of the work by Shandley et al. (2) lies in highlighting the need to consider additional reproductive comorbidities other than decreased ovarian reserve in the clinical care of young female cancer survivors.

This analysis of the Furthering Understanding of Cancer, Health, and Survivorship in Adult Women (FUSCHIA) study described infertility and ovarian reserve measures in young survivors with polycystic ovarian syndrome (PCOS). The FUSCHIA study is a population-based, retrospective cohort study that includes reproductive-aged female cancer survivors between 22 and 45 years old, who were diagnosed as young adults between ages 20 and 35 years, and similarly aged women without cancer. Among 1,090 survivors, 78 (7.2%) self-reported that a medical professional had diagnosed them with PCOS in the past, and about half of these women underwent gonadotoxic therapy, defined as systemic chemotherapy, total body irradiation, or abdominopelvic radiation.

Infertility after cancer diagnosis occurred more frequently in survivors with PCOS than survivors without PCOS, despite the finding that survivors with PCOS were younger and had higher antimüllerian hormone levels and antral follicle counts. Twenty-three percent of survivors with PCOS reported infertility after their cancer diagnosis, compared to 14% survivors without PCOS (adjusted odds ratio 2.2, 95% confidence interval 1.2, 4.1). Survivors with PCOS also reported longer time to pregnancy. It is not clear why they were at higher risk of infertility, but the results support that decreased ovarian reserve is likely not the leading etiology. One clear possibility is oligoovulation and anovulation, which could not be confirmed because of the retrospective nature of this study with a lack of menstrual or biomarker data from when infertility occurred. A second possibility is confounding by indication. Polycystic ovarian syndrome was more frequently diagnosed in women who presented with infertility and had a subsequent workup and healthcare provider diagnosis than in women who were not infertile and did not undergo evaluation. Nonetheless, these findings bring forth the notion that infertility in cancer survivors is not solely due to ovarian senescence. In the clinical setting, other causes of infertility need to be considered in cancer survivors, not only for appropriate fertility management, but also for implementing relevant screening and follow-up, such as for diabetes in PCOS. In research, more data like these are needed on the magnitude of infertility risk in survivors diagnosed as young adults rather than in childhood, as well as more clarity on the different causes of infertility within the heterogeneous population.

A second interesting observation was less infertility after cancer in survivors with PCOS who underwent gonadotoxic therapy than in survivors with PCOS who did not undergo gonadotoxic therapy. In the subset of survivors who underwent ovarian reserve measurements, antimüllerian hormone levels and antral follicle counts were lower, as expected, in women who were exposed to gonadotoxins compared with women who were not exposed. The investigators hypothesize that a similar effect to ovarian drilling occurred with radiation or chemotherapy. Ovarian drilling has been used as an intervention to improve fertility by increasing ovulation in anovulatory women with PCOS. One reported mechanism for improving ovulation has been follicle destruction, resulting in a decrease in local androgens and altering feedback to central gonadotropins. This mechanism would be consistent with improving short-term fertility outcomes—the focus of most studies on ovarian drilling, but is less relevant to cancer survivors who often have a significant waiting period after cancer diagnosis before attempting pregnancy. There are some longitudinal data that support that favorable endocrine profiles are sustained years after ovarian drilling (3). A second pathway is simply accelerated loss of ovarian reserve, consistent with the observation that anovulation decreases and menstrual cycles become more regular as women with PCOS age (4). Finally, the ovarian cortex of women with PCOS has been described as thickened with increased collagen, which may mechanically impact ovulation. As radiation causes significant fibrosis to tissue, it would be interesting to compare, in a larger population, differences in radiation versus systemic chemotherapy in their association with oligoovulation or anovulation and infertility in cancer survivors with and without PCOS.

Young women who have had cancer wish to have biologic children. This study contributes invaluable data on the extent to which women who are diagnosed as young adults experience infertility and do not meet their reproductive goals. There is no question that clinical care of these individuals can be complex, but herein lies the role of the reproductive specialists in cancer survivorship care, contributing our expertise in reproductive comorbidities to improve care of and overall quality of life for young adult cancer survivors.

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