ONLINE EXCLUSIVE

# Chronic Stress and Ovarian Function in Female Childhood Cancer Survivors

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**OBJECTIVES:** To explore the relationships among perceived stress, biomarkers of hypothalamic–pituitary–adrenal (HPA) activity, gonadotropin levels, and anti-Müllerian hormone (AMH) in female childhood cancer survivors (CCSs).

**SAMPLE & SETTING:** 24 female CCSs from the Royal Hospital for Sick Children in Edinburgh, Scotland, were included in the study.

**METHODS & VARIABLES:** Perceived stress was measured using the Perceived Stress Scale. HPA activity was measured using salivary cortisol and hair cortisol. Ovarian function was measured using serum gonadotropin levels and serum AMH levels. Latent growth curve modeling was used to determine diurnal cortisol slope and intercept. Bayesian structural equation modeling was used to explore the relationship among perceived stress, biomarkers of HPA activity, and ovarian function.

**RESULTS:** The authors found an inverse association between perceived stress and ovarian function and a positive association between biomarkers of HPA activity and ovarian function.

**IMPLICATIONS FOR NURSING:** Further research is needed to understand factors contributing to risk for post-treatment reproductive dysfunction in female CCSs.

**KEYWORDS** childhood cancer survivors; ovarian function; biomarkers; perceived stress
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An estimated 1 in 1,000 adults aged younger than 35 years is a survivor of childhood cancer (Blumenfeld, 2012). Because of significant advances in the treatment of pediatric cancer, the five-year survival rate exceeds 80% in the United States (Phillips et al., 2015). With an increasing number of survivors, there has been growing recognition of the late effects of cancer treatment (Kremer et al., 2013). Among these, reproductive dysfunction is a major concern for cancer survivors and is highly correlated with quality of life in this population (Cherven, Mertens, Wasilewski-Masker, Williamson, & Meacham, 2015; Knopman, Papadopoulos, Grifo, Fino, & Noyes, 2010; Kondapalli et al., 2014; Letourneau, Chan, & Rosen, 2013). Among female childhood cancer survivors (CCSs), 6% experience acute ovarian failure, and another 23% experience a significant reduction in ovarian function (Salih et al., 2015).

In clinical practice, post-treatment ovarian function is assessed using a profile of hormones, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH), plus the presence or absence of menses. However, neither FSH nor menstrual cyclicity post–cancer treatment are reliable predictors of future fertility (Knight et al., 2015). Because risk of infertility related to premature ovarian failure is associated with the size of the ovarian follicle pool (ovarian reserve), a biomarker that more closely reflects the number of remaining follicles in the ovary would have significant clinical potential. Anti-Müllerian hormone (AMH) is a biomarker of the ovarian reserve; plasma levels reflect the continuous noncyclic growth of small follicles and, therefore, mirror the size of the remaining follicle pool (Jeppesen et al., 2013). AMH is prematurely reduced in CCSs (Anderson & Wallace, 2013; Charpentier et al., 2014; Miyoshi et al., 2013) and may be an early marker of significant gonadotoxicity post-treatment (Brougham et al., 2012; Lie Fong et al., 2009). Although studies have demonstrated the use of pretreatment