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RESEARCH

Anti-Müllerian Hormone Levels and Urinary Cortisol in Women With Chronic Abdominal Pain

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ABSTRACT

Objective: To explore the association of hypothalamic–pituitary–adrenal activity with ovarian functioning in women with and without chronic abdominal pain (CAP).

Design and Setting: A secondary data analysis was performed with data from female participants in a natural history protocol at the National Institutes of Health.

Participants: A total of 36 women (age range = 19–39 years, mean = 27.11 years) were included in the study.

Methods: This pilot study was conducted with a subset of participants enrolled in a natural history protocol conducted in the Hatfield Clinical Research Center at the National Institutes of Health. The parent study included participants with and without CAP who provided a 5-hour urine sample for determination of cortisol levels and serum samples for determination of circulating levels of cortisol, luteinizing hormone, and follicle-stimulating hormone. CAP was defined as presence or absence of chronic pain for at least 6 months and was determined via self-report.

Results: Anti-Müllerian hormone (AMH) concentrations declined significantly with age as expected. When AMH levels were dichotomized as *normal* or *abnormal* (defined as higher or lower than age-specific normative ranges, respectively), there were significant associations between abnormal AMH levels and CAP and urine cortisol levels. Participants with CAP or low urine cortisol levels were significantly more likely to have abnormal AMH levels.

Conclusion: Results suggest that chronic abdominal pain and hypothalamic–pituitary–adrenal dysregulation may be associated with abnormal AMH levels.

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One in ten women faces early ovarian senescence, which means that around 10% of women will experience fertility problems related to diminished ovarian reserve by their early to mid-thirties (Maheshwari, Bhattacharya, & Johnson, 2008). Ovarian reserve, the number of remaining follicles in the ovary, declines naturally with age; however, researchers recently showed that age alone is not an accurate indicator of reproductive age and that other factors may be implicated in the depletion of the ovarian follicle pool (van Disseldorp et al., 2008). Thus, the identification of factors that contribute to the decline of ovarian reserve may aid in the prevention and early detection of follicular depletion, premature ovarian failure, and impaired fertility (Lie Fong et al., 2009).

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis accelerates biological aging and may contribute to ovarian senescence (Miller, Chen, & Parker, 2011; Révész et al., 2014). Chronic physiologic stress, such as chronic abdominal pain (CAP) can lead to HPA dysregulation (Révész et al., 2014). Women report CAP more frequently than men in the United States (2:1), and CAP is estimated to occur in 14% of women worldwide (Lovell & Ford, 2012; Peace et al., 2012). Individuals with chronic pain often exhibit HPA dysregulation (Simons, Elman, & Borsook, 2014; Vachon-Presseau et al., 2013), and for this reason, CAP is an ideal model to explore the influence of HPA activity on ovarian function. In this pilot study, we explored the association between chronic pain, a model of HPA dysregulation, and ovarian reserve.

Anti-Müllerian Hormone: A Measure of Ovarian Reserve

Anti-Müllerian hormone (AMH) is produced by the granulosa cells of growing ovarian follicles until

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The identification of factors that contribute to the decline of ovarian reserve may help detect and prevent follicular depletion, premature ovarian failure, and impaired fertility.

they have reached the size and differentiation state at which they may be selected for dominance (La Marca et al., 2012). Kelsey, Wright, Nelson, Anderson, and Wallace (2011) validated serum AMH as a biomarker of ovarian reserve and showed changes in AMH levels throughout a female's lifespan. AMH levels steadily increase from conception, reach their peak at 24.5 years of age, and then steadily decline until menopause (Kelsey et al., 2011). Two properties of AMH make it particularly useful in the study of ovarian reserve: the decline of AMH levels in serum is the earliest indication of a decline in ovarian reserve, and AMH levels remain stable throughout the menstrual cycle (Shaw et al., 2011).

AMH has been used to predict ovarian response to reproductive assistive technologies and to determine the effect of chemotherapy and radiation on ovarian function. More recent data supported the association between AMH and the onset of menopause, significantly expanding the potential application of this measure as a biomarker of ovarian function (van Disseldorp et al., 2008). Factors associated with lower serum concentrations are obesity (Malhotra, Bahadur, Singh, Kalaivani, & Mittal, 2013; Steiner, Stanczyk, Patel, & Edelman, 2010), oral contraceptive use, (Dewailly et al., 2014; Steiner et al., 2010), and pregnancy (Nelson, Stewart, Fleming, & Freeman, 2010). However, it is not known if chronic pain or HPA dysregulation affect ovarian reserve.

HPA Dysregulation, Stress, and Ovarian Function

HPA dysregulation due to repeated or prolonged stressors, such as chronic pain, stimulates cortisol secretion, reducing pulsatile luteinizing hormone (LH) secretion and interrupting the follicular phase of the menstrual cycle (Breen & Mellon, 2014). At homeostatic levels, cortisol contributes to steroid biosynthesis and maintenance of gonadotropin release; elevated cortisol levels suppress gonadotropin-releasing hormone secretion at the level of the pituitary and increases rates of follicle atresia (Whirledge & Cidlowski, 2010; Whirledge & Cidlowski, 2013).

Allsworth, Zierler, Krieger, and Harlow (2001) were among the first to investigate the effect of chronic stress on ovarian reserve. They examined whether ovarian hormone levels (follicle-stimulating hormone [FSH] and estradiol) indicative of menopausal changes were observed at an earlier age among 732 women (ages 36–44 years) who experienced physical or sexual violence compared with women who reported no exposure to violence. More extreme levels of FSH and estradiol in relation to abuse history among premenopausal women ages 41–45 years were observed, whereas little difference was seen for younger women. Allsworth et al. offered a potential biological explanation for the association between abuse history and ovarian function: stress activates the HPA axis and stimulates glucocorticoid secretion, which in turn inhibits the synthesis and release of gonadotropin-releasing hormone, LH, and FSH. However, Allsworth et al. did not include a biomarker of stress in the study and, as a result, were unable to examine this proposed biological mechanism.

Pal, Bevilacqua, and Santoro (2010) expanded the work of Allsworth et al. (2001) and examined associations between acute (serum cortisol) and chronic (history of abuse and/or drug use) psychosocial stress and biomarkers of ovarian reserve (FSH and Müllerian-inhibiting substance [now referred to as AMH]) in 89 premenopausal women with infertility who were younger than 42 years. Women were considered to have diminished ovarian reserve (DOR) if they had early follicular phase (days 1–3) FSH levels greater than 10 mIU/ml and/or poor ovarian response during attempts at ovarian hyperstimulation. Those with chronic stress had reduced ovarian reserve parameters: higher FSH level ($p = .051$) and significantly lower Müllerian-inhibiting substance levels ($p = .034$) and were 3 times more likely to have a diagnosis of DOR ($p = .025$). However, no association was observed between serum cortisol levels and DOR. Pal et al. concluded that chronic but not current stress was associated with DOR. They proposed inappropriate HPA activation as a plausible explanation for this association. Because a biomarker of chronic stress was not included in the study, they were unable to provide evidence to support this theory.

Although it is well established that psychological stress interrupts normal reproductive functioning (An, Sun, Li, Zhang, & Ji, 2013; Kalantaridou et al., 2010; O'Connor et al., 2011; Whirledge &

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