JOGNN

CrossMark

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

Theresa M. Hardy, Donna O. McCarthy, Nicolaas H. Fourie, and Wendy A. Henderson

Correspondence
Wendy A. Henderson, PhD, MSN, CRNP, Division of Intramural Research, National Institute of Nursing Research, National Institutes of Health, 10 Center Drive, 2-1341, Bethesda, MD 20892.
hendersw@mail.nih.gov

Keywords
AMH
chronic abdominal pain
ovarian reserve
reproductive health

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.

Theresa M. Hardy, BSN, is a doctoral student in the College of Nursing, Marquette University, Milwaukee, WI.

Donna O. McCarthy, PhD, RN, FAAN, is a professor and Interim Dean of the College of Nursing, Marquette University, Milwaukee, WI.

Nicolaas H. Fourie, PhD, is a research fellow in the Division of Intramural Research, National Institute of Nursing Research, Bethesda, MD.

(Continued)

AWHONN

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

Hardy, T. M., McCarthy, D. O., Fourie, N. H., and Henderson, W. A.

RESEARCH

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)

> **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.**

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 &

Wendy A. Henderson, PhD, MSN, CRNP, is an investigator in the Biobehavioral Branch and Chief of the Digestive Disorders Unit, Division of Intramural Research, National Institute of Nursing Research, Bethesda, MD.

Cidlowski, 2013), the biological mechanisms underlying this effect are poorly understood (Bleil et al., 2012a, 2012b; Lynch, Sundaram, Buck Louis, Lum, & Pyper, 2012). Our purpose in this pilot study was to explore the association between HPA activity and ovarian reserve (as measured by AMH concentrations) in women with CAP. Because CAP is associated with HPA dysregulation, we hypothesized that women with CAP would exhibit abnormal AMH concentrations.

Theoretical Framework

The theoretical framework used to guide this study was life history (Whirledge & Cidlowski, 2013). Life history theory posits that the allocation of biological resources is a trade-off between survival and reproduction. The intrinsic and extrinsic environments of the organism influence the timing of puberty, fertility outcomes, and reproductive lifespan. The division of resources is mediated through HPA activation. HPA activation leads to an increase in glucocorticoids, directing resources to vital physiologic activities such as energy mobilization, cardiac output, and cognition. At normal physiologic levels, glucocorticoids promote reproductive function, but in circumstances of prolonged stress, such as chronic pain, prolonged exposure to increased levels of glucocorticoids suppresses gonadotropin release.

Methods

Study Population

The protocol was approved by the institutional review board at the National Institutes of Health (Clinicaltrial.gov #NCT00824941). This pilot study was conducted using a subset of participants enrolled in a natural history protocol (Clinicaltrial.gov #NCT00824941) conducted in the Hatfield Clinical Research Center at the National Institutes of Health. The parent study included participants who completed the Sociodemographic Questionnaire developed by the Center for Research in Chronic Disorders, University of Pittsburgh School of Nursing (1999) and provided urine and serum samples. For this pilot study, only women between the ages of 19 and 39 years who had their menses for at least 2 years were included. Exclusion criteria were history of organic gastrointestinal disease; cardiac, pulmonary, neurologic, renal, endocrine, or gynecologic pathology; taking medications for gastrointestinal symptoms daily or other medications that would alter serotonin, catecholamines, or cortisol; work during the late evening and night shifts; severe comorbid pain or

psychiatric conditions; intake of more than 300 mg of caffeine-containing beverages or food in the afternoon/evening or more than 2 servings of alcohol-containing beverages every day; unable to physically use the touch screen for the purpose of the study; visually impaired or institutionalized; or pregnant or lactating. A total of 36 women (33.3% Black or African American, 47.2% White, 19.4% Asian/other ethnicity) between the ages of 19 and 39 years with mean age 27.11 ± 5.03 were included in the study. All participants were between days 3 and 7 of their menstrual cycles.

Data Collection

Participants enrolled in the parent study completed the sociodemographic questionnaire electronically. Whole blood was collected between the hours of 0800 and 1000, and a 5-hour urine sample was collected between the hours of 1000 and 1500. Whole-body air displacement plethysmography, which is used to measure body fat percentage, was completed on all participants. Body fat of 30% or greater was categorized as *high body fat* and less than 30% as *low body fat.* Urine cortisol was measured via liquid chromatography–tandem mass spectrometry. Cortisol secretion follows a diurnal pattern, and levels peak in the morning and steadily decrease throughout the day (Hannibal & Bishop, 2014). Thus, 5-hour urine cortisol test results reflect a time-averaged measure of adrenocortical function. Serum was analyzed for circulating levels of cortisol, FSH, and LH. CAP was defined as self-reported presence or absence of abdominal pain for at least 6 months and was confirmed during the clinical visit by using the Gastrointestinal Pain Pointer (Henderson et al., 2015).

AMH

For this pilot study, in addition to the measures included in the parent study as described earlier, the AMH Gen II ELISA (Beckman Coulter, Inc., Brea, CA) was used to measure AMH concentrations in stored serum samples of 36 women per the manufacturer's instructions. The AMH Gen II ELISA has a sensitivity of 0.57 pmol/l, and the intra-assay coefficient of variation was 4.5%. The validated model of serum AMH by Kelsey et al. (2011) and the nomogram with normative values for age published by La Marca et al. (2012) were used to interpret AMH levels. Continuous AMH levels were used to investigate associations between AMH, CAP, serum and urinary cortisol, and body fat. A dichotomous AMH variable

Table 1: Clinical and Demographic Data

Characteristic	Overall (n = 36)	Pain (n = 17)	No Pain (n =19)	p	High Body Fat (n = 22)	Low Body Fat (n = 14)	p
Age in years	27.11 ± 5.03	28 ± 3.82	26.32 ± 5.9	.310	28.64 ± 4.87	24.71 ± 4.44	.019[*]
% body fat	31.99 ± 8.85	33.83 ± 7.76	30.13 ± 9.77	.220	37.68 ± 5.71	22.75 ± 4.05	<.001[***]
FSH level (U/L)	4.50 ± 2.14	4.5 ± 2.44	4.51 ± 1.96	.990	4.84 ± 2.2	3.99 ± 2.08	.250
LH level (U/L)	3.64 ± 2.66	2.65 ± 2.25	4.38 ± 2.78	.048[*]	3.46 ± 2.42	3.72 ± 3.08	.790
Serum cortisol (μg/dl)	11.06 ± 4.85	12.14 ± 5.27	10.26 ± 4.49	.260	10.76 ± 4.59	11.75 ± 5.46	.580
Urine cortisol level (nmol)	40.68 ± 46.92	29.59 ± 29.17	51.16 ± 57.99	.022[*]	31.92 ± 27.01	55.51 ± 67.69	.090
AMH level (ng/ml)	4.05 ± 3.11	4.31 ± 4.16	3.81 ± 1.81	.504	3.9 ± 3.43	4.27 ± 2.64	.290
	Overall (n = 36)	OC Use (n = 12)	No OC Use (n = 24)	p	Abnormal AMH (n = 5)	Normal AMH (n = 31)	p
Age in years	27.11 ± 5.03	26.17 ± 3.76	27.58 ± 5.57	.510	29 ± 2.92	26.81 ± 5.26	.320
% body fat	31.99 ± 8.85	29.6 ± 7.8	33.02 ± 9.43	.370	34.68 ± 9.43	31.42 ± 8.95	.410
FSH level (U/L)	4.50 ± 2.14	2.99 ± 1.93	5.26 ± 1.89	.002[**]	3.68 ± 1.68	4.64 ± 2.23	.340
LH level (U/L)	3.64 ± 2.66	1.58 ± 2.34	4.56 ± 2.24	<.001[***]	3.87 ± 2.7	1.68 ± 1.29	.120
Serum cortisol level (μg/dl)	11.06 ± 4.85	16.28 ± 3.63	8.58 ± 3.09	<.001[***]	13.28 ± 5.37	10.8 ± 4.82	.340
Urine cortisol level (nmol)	40.68 ± 46.92	32.88 ± 23.41	44.75 ± 55.48	.870	16.64 ± 10.94	44.69 ± 49.48	.040[*]
AMH level (ng/ml)	4.05 ± 3.11	4.47 ± 4.5	3.83 ± 2.21	.810	5.88 ± 7.13	3.75 ± 1.97	.490

Note. AMH = Anti-Müllerian hormone; FSH = follicle stimulating hormone; LH = luteinizing hormone; OC = oral contraceptive.
[*]p < .05. [**]p < .01. [***]p < .001.

Hypothalamic–pituitary–adrenal dysregulation may contribute to ovarian dysfunction as expressed by abnormal anti-Müllerian hormone levels in women with chronic abdominal pain.

(*normal* or *abnormal*) was also created for contingency analysis. Abnormal AMH values were defined as values that fell above or below the normative age-specific ranges published by La Marca et al.

Statistical Analysis

Descriptive analyses were performed for demographic variables using grouping factors: high (≥30%) and low (<30%) body fat, presence or absence of CAP, oral contraceptive use, and AMH category (normal or abnormal). Body fat (Freeman et al., 2007; Malhotra et al., 2013; Steiner et al., 2010) and oral contraceptive use (La Marca et al., 2010; Shaw et al., 2011) were included as grouping factors in the descriptive analysis because of prior evidence of their association with abnormal AMH levels. CAP was included to explore differences between participants with and without chronic pain.

Multiple linear regression was used to explore associations between serum AMH concentration and serum and urine cortisol, FSH and LH, body fat, and CAP with and without adjusting for age as a covariate in the model. A contingency analysis was also conducted to evaluate the association between categorized AMH levels (normal or abnormal) and CAP (yes or no) and serum and urine cortisol, respectively. All p values of .05 or less were considered statistically significant, and no adjustment for multiplicity was made. Mean ± standard deviation were used to report the average and dispersion, unless otherwise specified. Analysis was performed using SPSS version 15 and JMP version 11.

Results

There were significant differences in laboratory and demographic data between selected grouping factors (Table 1). Participants with CAP had lower urine cortisol levels ($p = .02$) and LH levels ($p = .048$) than those without CAP. Participants with high body fat were older than participants with low body fat ($p = .03$). Those who used oral contraceptives had significantly lower

FSH ($p = .002$) and LH ($p ≤ .001$) and higher serum cortisol levels ($p ≤ .001$).

CAP was negatively associated with urine cortisol levels ($p = .02$). Participants with CAP also had significantly lower LH levels. As expected, oral contraceptive use was associated with lower LH and FSH levels. Oral contraceptive use was also associated with higher serum cortisol levels. Previous studies have shown this association; exogenous estrogens in oral contraceptive pills increase corticosteroid-binding globulin and total plasma cortisol concentrations (Jung et al., 2011).

Serum AMH concentrations were negatively correlated with age as expected ($r = -.423$, $p = .01$). Serum AMH, with and without adjusting for age, was not associated with CAP, urine and serum cortisol, and body fat. However, when AMH was categorized as normal or abnormal (La Marca et al., 2012), a contingency table analysis showed that serum AMH was associated with CAP and 5-hour urinary cortisol level. Participants with abnormal AMH levels ($n = 5$) were more likely to have CAP (100% vs. 38%, $p = .01$) than those with normal AMH levels ($n = 31$). Participants with abnormal AMH levels were also more likely to have a lower 5-hour urine cortisol level (16 ± 11 vs. 45 ± 49, $p = .04$) than those with normal AMH levels (Figure 1). AMH (normal or abnormal) was not associated with body fat percentage ($p = .41$) or serum cortisol ($p = .34$).

Discussion

We found that urine cortisol levels were lower in women with CAP. Others have reported that chronic stress, including chronic pain, is associated with lower or blunted cortisol levels (Generaal et al., 2014; Juster et al., 2011; Suzuki, Poon, Papadopoulos, Kumari, & Cleare, 2014; Voellmin et al., 2015). The lower levels of urine cortisol observed in participants with CAP supports our premise that CAP leads to HPA dysregulation. CAP was also associated with lower LH levels. Others have shown that chronic stress suppresses LH levels, validating that CAP is a chronic stressor (Breen, Billings, Wagenmaker, Wessinger, & Karsch, 2005). Abnormal AMH levels were significantly associated with the presence of CAP and lower urine cortisol levels. These findings suggest that CAP may alter HPA activity, as expressed by lower urine cortisol levels in women with CAP. HPA dysregulation may contribute to ovarian dysfunction as expressed by abnormal AMH levels in women with chronic abdominal pain. Authors of

previous studies have shown that cortisol has stimulatory and inhibitory effects on the ovary (Whirledge & Cidlowski, 2013).

Further research is needed to clarify the association between chronic physiologic and psychological stressors, such as chronic pain and ovarian function. Understanding the biobehevioral mechanism behind this association will improve the ability to identify and prevent a modifiable risk factor of premature ovarian aging. Authors of several studies have reported negative associations between daily/acute stress levels and reproductive function. Schliep et al. (2015) found that high daily stress was associated with lower estradiol and LH, as well as with higher FSH. Daily stress was also associated with lower luteal phase progesterone and higher odds of anovulation. Conversely, Bleil et al. (2012b) found that psychological stress was related to higher antral follicle count, a measure of ovarian reserve, among younger women and greater antral follicle count decline across women. They proposed a model by which high stress promotes reproductive readiness in the short term (i.e., increased number of developing follicles) at the cost of prematurely depleting the ovarian follicle pool over time (Bleil et al., 2012b).

Within the context of in vitro fertilization, stress has been associated with reduced chances to achieve a successful pregnancy (Ebbesen et al., 2009; Lynch, Sundaram, Maisog, Sweeney, & Buck

> **Anti-Müllerian hormone, as a measure of ovarian reserve, may offer valuable insight into the enduring effects of hypothalamic–pituitary–adrenal activity on the reproductive system.**

Louis, 2014), and the incorporation of stress reduction interventions may improve fertility outcomes (Catherino, 2011). However, most studies examining this association have been in populations with infertility who undergo assistive reproductive treatments, and for this reason, it is unclear whether stress is a biobehavioral risk factor for the development of infertility or is secondary to an infertility diagnosis. Improved comprehension of the effect of prolonged stress on ovarian function will increase our ability to counsel those for whom stress may lead to premature ovarian aging and an increased risk of infertility.

We also found that body fat and oral contraceptive use were not associated with abnormal AMH levels. Although these findings contradict the results of prior studies (Freeman et al., 2007; Steiner et al., 2010), this may be due to the relatively small sample size and the limited range in body fat percentages. In addition to these main findings, we demonstrated, to our knowledge, an innovative way to examine the relationship between AMH and other factors thought to affect ovarian function. Previous researchers have
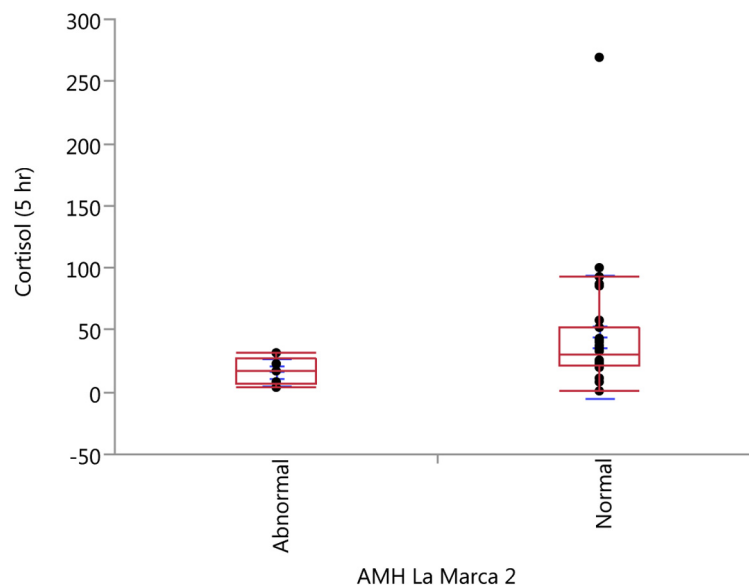
Figure 1. Urine cortisol level (5 hour) for women with normal and abnormal AMH (La Marca et al., 2012). AMH = anti-Müllerian hormone; hr = hour.

examined AMH as a continuous variable; however, any AMH value that falls outside the normative age-specific range (too high or too low) is considered abnormal in the clinical setting. This would suggest that predictors of abnormal AMH levels might be more accurately identified through an analysis of AMH as a categorical variable (normal or abnormal). Additional studies are warranted to confirm the usefulness of this statistical approach in future research and clinical practice.

Limitations

The study has several limitations. Because the study was an exploratory study that used data collected from a subset of participants who met specific inclusion/exclusion criteria, the sample size is small. Another limitation was that we relied on cross-sectional data. To achieve a more precise representation of the effect of chronic stress, such as CAP, on reproductive health, further studies will require the use of a longitudinal design in which AMH levels are measured at various intervals across the menstrual cycle and symptom experience. Finally, CAP was measured using self-report, which is subjective. However, because individuals with CAP do not have a consistent pain experience, we did not collect data on participants' current level of pain at the time of enrollment in the study.

Conclusion

Because knowledge of factors that affect ovarian reserve is incomplete, AMH may be a useful tool to aid in the assessment of ovarian functioning. Because this was a pilot study, we believe the data support the idea that HPA dysregulation may affect ovarian function. AMH, as measure of ovarian reserve, may offer valuable insight into the enduring effects of HPA activity on the reproductive system. More research is needed to answer pressing clinical questions to improve nursing practice for the care of women who experience reproductive health issues.

Acknowledgment

The opinions expressed herein and the interpretation and reporting of these data are the responsibility of the author(s) and should not be seen as an official recommendation, interpretation, or policy of the National Institutes of Health or the United States Government.

REFERENCES

Allsworth, J. E., Zierler, S., Krieger, N., & Harlow, B. L. (2001). Ovarian function in late reproductive years in relation to lifetime experiences of abuse. *Epidemiology, 12*(6), 676–681.

An, Y., Sun, Z., Li, L., Zhang, Y., & Ji, H. (2013). Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: Psychological and neurohormonal assessment. *Journal of Assisted Reproduction and Genetics, 30*(1), 35–41. http://dx.doi.org/10.1007/s10815-012-9904-x

Bleil, M. E., Adler, N. E., Pasch, L. A., Sternfeld, B., Gregorich, S. E., Rosen, M. P., & Cedars, M. I. (2012a). Depressive symptomatology, psychological stress, and ovarian reserve: A role for psychological factors in ovarian aging? *Menopause, 19*(11), 1176–1185. http://dx.doi.org/10.1097/gme.0b013e31825540d8

Bleil, M. E., Adler, N. E., Pasch, L. A., Sternfeld, B., Gregorich, S. E., Rosen, M. P., & Cedars, M. I. (2012b). Psychological stress and reproductive aging among pre-menopausal women. *Human Reproduction, 27*(9), 2720–2728. http://dx.doi.org/10.1093/humrep/des214

Breen, K. M., Billings, H. J., Wagenmaker, E. R., Wessinger, E. W., & Karsch, F. J. (2005). Endocrine basis for disruptive effects of cortisol on preovulatory events. *Endocrinology, 146*(4), 2107–2115. http://dx.doi.org/10.1210/en.2004-1457

Breen, K. M., & Mellon, P. L. (2014). Influence of stress-induced intermediates on gonadotropin gene expression in gonadotrope cells. *Molecular and Cellular Endocrinology, 385*(1–2), 71–77. http://dx.doi.org/10.1016/j.mce.2013.08.014

Catherino, W. H. (2011). Stress relief to augment fertility: The pressure mounts. *Fertility and Sterility, 95*(8), 2462–2463. http://dx.doi.org/10.1016/j.fertnstert.2011.05.067

Dewailly, D., Andersen, C. Y., Balen, A., Broekmans, F., Dilaver, N., Fanchin, R., … Anderson, R. A. (2014). The physiology and clinical utility of anti-Mullerian hormone in women. *Human Reproduction Update, 20*(3), 370–385. http://dx.doi.org/10.1093/humupd/dmt062

Ebbesen, S. M. S., Zachariae, R., Mehlsen, M. Y., Thomsen, D., Højgaard, A., Ottosen, L., … Ingerslev, H. J. (2009). Stressful life events are associated with a poor in-vitro fertilization (IVF) outcome: A prospective study. *Human Reproduction, 24*(9), 2173–2182. http://dx.doi.org/10.1093/humrep/dep185

Freeman, E. W., Gracia, C. R., Sammel, M. D., Lin, H., Lim, L. C.-L., & Strauss, J. F. (2007). Association of anti-Mullerian hormone levels with obesity in late reproductive-age women. *Fertility and Sterility, 87*(1), 101–106. http://dx.doi.org/10.1016/j.fertnstert.2006.05.074

Generaal, E., Vogelzangs, N., Macfarlane, G. J., Geenen, R., Smit, J. H., Penninx, B. W. J. H., & Dekker, J. (2014). Reduced hypothalamic-pituitary-adrenal axis activity in chronic multi-site musculoskeletal pain: Partly masked by depressive and anxiety disorders. *BMC Musculoskeletal Disorders, 15*(1), 227. http://dx.doi.org/10.1186/1471-2474-15-227

Hannibal, K. E., & Bishop, M. D. (2014). Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Physical Therapy, 94*(12), 1816–1825. http://dx.doi.org/10.2522/ptj.20130597

Henderson, W. A., Rahim-Williams, B., Kim, K. H., Sherwin, L. B., Abey, S. K., Martino, A. C., … Zuccolotto, A. P. (2015). The gastrointestinal pain pointer. *Gastroenterology Nursing. Advance online publication.* http://dx.doi.org/10.1097/SGA.0000000000000210

Jung, C., Ho, J. T., Torpy, D. J., Rogers, A., Doogue, M., Lewis, J. G., … Inder, W. J. (2011). A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. *Journal of Clinical Endocrinology and Metabolism, 96*(5), 1533–1540. http://dx.doi.org/10.1210/jc.2010-2395

Juster, R.-P., Sindi, S., Marin, M.-F., Perna, A., Hashemi, A., Pruessner, J. C., & Lupien, S. J. (2011). A clinical allostatic load index is associated with burnout symptoms and hypocortisolemic profiles in healthy workers. *Psychoneuroendocrinology, 36*(6), 797–805. http://dx.doi.org/10.1016/j.psyneuen.2010.11.001

Kalantaridou, S. N., Zoumakis, E., Makrigiannakis, A., Lavasidis, L. G., Vrekoussis, T., & Chrousos, G. P. (2010). Corticotropin-releasing hormone, stress and human reproduction: An update. *Journal of Reproductive Immunology, 85*(1), 33–39. http://dx.doi.org/10.1016/j.jri.2010.02.005

Kelsey, T. W., Wright, P., Nelson, S. M., Anderson, R. A., & Wallace, W. H. B. (2011). A validated model of serum anti-Müllerian hormone from conception to menopause. *PLOS ONE, 6*(7), e22024. http://dx.doi.org/10.1371/journal.pone.0022024

La Marca, A., Sighinolfi, G., Giulini, S., Traglia, M., Argento, C., Sala, C., … Toniolo, D. (2010). Normal serum concentrations of anti-Müllerian hormone in women with regular menstrual cycles. *Reproductive Biomedicine Online, 21*(4), 463–469. http://dx.doi.org/10.1016/j.rbmo.2010.05.009

La Marca, A., Spada, E., Grisendi, V., Argento, C., Papaleo, E., Milani, S., & Volpe, A. (2012). Normal serum anti-Müllerian hormone levels in the general female population and the relationship with reproductive history. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 163*(2), 180–184. http://dx.doi.org/10.1016/j.ejogrb.2012.04.013

Lie Fong, S., Laven, J. S., Hakvoort-Cammel, F. G., Schipper, I., Visser, J. A., Themmen, A. P., … van den Heuvel-Eibrink, M. M. (2009). Assessment of ovarian reserve in adult childhood cancer survivors using anti-Müllerian hormone. *Human Reproduction, 24*(4), 982–990. http://dx.doi.org/10.1093/humrep/den487

Lovell, R. M., & Ford, A. C. (2012). Effect of gender on prevalence of irritable bowel syndrome in the community: Systematic review and meta-analysis. *The American Journal of Gastroenterology, 107*(7), 991–1000. http://dx.doi.org/10.1038/ajg.2012.131

Lynch, C. D., Sundaram, R., Buck Louis, G. M., Lum, K. J., & Pyper, C. (2012). Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity? *Fertility and Sterility, 98*(2), 453–458. http://dx.doi.org/10.1016/j.fertnstert.2012.05.018

Lynch, C. D., Sundaram, R., Maisog, J. M., Sweeney, A. M., & Buck Louis, G. M. (2014). Preconception stress increases the risk of infertility: Results from a couple-based prospective cohort study—The LIFE study. *Human Reproduction, 29*(5), 1067–1075. http://dx.doi.org/10.1093/humrep/deu032

Maheshwari, A., Bhattacharya, S., & Johnson, N. P. (2008). Predicting fertility. *Human Fertility, 11*(2), 109–117. http://dx.doi.org/10.1080/14647270701832346

Malhotra, N., Bahadur, A., Singh, N., Kalaivani, M., & Mittal, S. (2013). Does obesity compromise ovarian reserve markers? A

clinician's perspective. *Archives of Gynecology and Obstetrics, 287*(1), 161–166. http://dx.doi.org/10.1007/s00404-012-2528-7

Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin, 137*(6), 959–997. http://dx.doi.org/10.1037/a0024768

Nelson, S. M., Stewart, F., Fleming, R., & Freeman, D. J. (2010). Longitudinal assessment of antimüllerian hormone during pregnancy-relationship with maternal adiposity, insulin, and adiponectin. *Fertility and Sterility, 93*(4), 1356–1358. http://dx.doi.org/10.1016/j.fertnstert.2009.07.1676

O'Connor, K. A., Brindle, E., Shofer, J., Trumble, B. C., Aranda, J. D., Rice, K., & Tatar, M. (2011). The effects of a long-term psychosocial stress on reproductive indicators in the baboon. *American Journal of Physical Anthropology, 145*(4), 629–638. http://dx.doi.org/10.1002/ajpa.21538

Pal, L., Bevilacqua, K., & Santoro, N. F. (2010). Chronic psychosocial stressors are detrimental to ovarian reserve: A study of infertile women. *Journal of Psychosomatic Obstetrics and Gynaecology, 31*(3), 130–139. http://dx.doi.org/10.3109/0167482X.2010.485258

Peace, R. M., Majors, B. L., Patel, N. S., Wang, D., Valle-Pinero, A. Y., Del Martino, A. C., & Henderson, W. A. (2012). Stress and gene expression of individuals with chronic abdominal pain. *Biological Research for Nursing, 14*(4), 405–411. http://dx.doi.org/10.1177/1099800412458350

Révész, D., Verhoeven, J. E., Milaneschi, Y., de Geus, E. J. C. N., Wolkowitz, O. M., & Penninx, B. W. J. H. (2014). Dysregulated physiological stress systems and accelerated cellular aging. *Neurobiology of Aging, 35*(6), 1422–1430. http://dx.doi.org/10.1016/j.neurobiolaging.2013.12.027

Schliep, K. C., Mumford, S. L., Vladutiu, C. J., Ahrens, K. A., Perkins, N. J., Sjaarda, L. A., … Schisterman, E. F. (2015). Perceived stress, reproductive hormones, and ovulatory function. *Epidemiology, 26*(2), 177–184. http://dx.doi.org/10.1097/EDE.0000000000000238

Shaw, C. M., Stanczyk, F. Z., Egleston, B. L., Kahle, L. L., Spittle, C. S., Godwin, A. K., … Dorgan, J. F. (2011). Serum Antimüllerian hormone in healthy premenopausal women. *Fertility and Sterility, 95*(8), 2718–2721. http://dx.doi.org/10.1016/j.fertnstert.2011.05.051

Simons, L. E., Elman, I., & Borsook, D. (2014). Psychological processing in chronic pain: A neural systems approach. *Neuroscience and Biobehavioral Reviews, 39*, 61–78. http://dx.doi.org/10.1016/j.neubiorev.2013.12.006

Steiner, A. Z., Stanczyk, F. Z., Patel, S., & Edelman, A. (2010). Antimüllerian hormone and obesity: Insights in oral contraceptive users. *Contraception, 81*(3), 245–248. http://dx.doi.org/10.1016/j.contraception.2009.10.004

Suzuki, A., Poon, L., Papadopoulos, A. S., Kumari, V., & Cleare, A. J. (2014). Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the occurrence of depression. *Psychoneuroendocrinology, 50*, 289–299. http://dx.doi.org/10.1016/j.psyneuen.2014.09.007

University of Pittsburgh School of Nursing. (1999). *Socio-demographic questionnaire.* Pittsburgh, PA: Center for Research in Chronic Disorders.

Vachon-Presseau, E., Roy, M., Martel, M. O., Caron, E., Marin, M. F., Chen, J., … Rainville, P. (2013). The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. *Brain, 136*(3), 815–827. http://dx.doi.org/10.1093/brain/aws371

van Disseldorp, J., Faddy, M. J., Themmen, A. P. N., de Jong, F. H., Peeters, P. H. M., van der Schouw, Y. T., & Broekmans, F. J. M. (2008). Relationship of serum antimüllerian hormone concentration to age at menopause. *Journal of Clinical Endocrinology*

and Metabolism, 93(6), 2129–2134. http://dx.doi.org/10.1210/jc.2007-2093

Voellmin, A., Winzeler, K., Hug, E., Wilhelm, F. H., Schaefer, V., Gaab, J., … Bader, K. (2015). Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity. *Psychoneuroendocrinology, 51*, 58–67. http://dx.doi.org/10.1016/j.psyneuen.2014.09.008

Whirledge, S., & Cidlowski, J. A. (2010). Glucocorticoids, stress, and fertility. *Minerva Endocrinologica, 35*(2), 109–125. http://dx.doi.org/10.1586/eem.10.1

Whirledge, S., & Cidlowski, J. A. (2013). A role for glucocorticoids in stress-impaired reproduction: beyond the hypothalamus and pituitary. *Endocrinology, 154*(12), 4450–4468. http://dx.doi.org/10.1210/en.2013-1652