The relationship between metabolic stress and Anti-Müllerian hormone (AMH) in women hospitalized in intensive care units.

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ABSTRACT

Objective: Our study aimed to investigate the levels of anti-Müllerian hormone (AMH) to determine ovarian reserve in women in intensive care units experiencing metabolic and physiological stress.

Materials and Methods: For this purpose, 37 women were hospitalized in the intensive care unit (ICU) of Siirt Training and Research Hospital between November 2022 and February 2023. The same number of healthy control groups were included in the study. Patient selection was based on acute physiology and chronic health assessment (APACHI II) score and injury severity score (ISS).Anti-müllerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), adrenocorticotropic hormone (ACTH), cortisol. , prolactin, C-reactive hormone (CRP) serum levels were examined

Results: There was no significant difference in mean age between intensive care patients (29.3±8.3 , n=37) and control group (28.0±0.0, n=37) (p=0.349). A statistically significant difference was found between the AMH values between the patients hospitalized in the intensive care unit and the control group (p=0.012).AMH values were significantly lower in ICU patients. However, the T3 value was observed to be significantly lower in ICU patients compared to the control group (p < 0.0001). Additionally, prolactin, CRP, and cortisol values were found to be statistically significantly higher.

Conclusion: This study revealed a significant decrease in anti-Müllerian hormone (AMH) levels among women experiencing metabolic and physiological stress in intensive care units. The lowered AMH levels suggest a potential impact on ovarian reserve in such conditions. Additionally, the observation of reduced T3 levels in ICU patients could indicate thyroid function alterations during times of stress. The elevated prolactin, CRP, and cortisol levels further underscore the physiological disruptions experienced by ICU patients. These findings emphasize the importance of considering hormonal and metabolic changes in critically ill women, particularly in relation to their ovarian health. Further research is warranted to elucidate the intricate mechanisms underlying these hormonal alterations and their potential long-term implications.

Keywords: anti-Müllerian hormone, AMH; ovarian , stress, physiological effects

INTRODUCTION

With changes in society, culture and living environment, women are more likely to suffer from psychophysiological health (1). Repeated and prolonged stress causes hypothalamic-pituitary-adrenal (HPA) dysregulation that disrupts homeostasis (2). Activation of the HPA axis results in the secretion of various stress hormones, including glucocorticoids, corticotropin-releasing factor (CRF), and cortisol (3).When the organism is exposed to a metabolic stress such as trauma, infection, surgery, it gives some metabolic, endocrine and immunological responses in order to maintain its balance.

It has been reported that hypothalamo-pituitary hormones, adrenocortical hormones, thyroid hormones, autonomic nervous system, arachidonic acid metabolites, opioids, cytokines, kallikrein kinin system play a role in this response (4). In the metabolic endocrine response to trauma, there is an increase in ACTH, cortisol, and growth hormone. It has been reported that there may be an increase or decrease in TSH, FSH and LH (6).

At the same time, the ovaries are the most dynamic organ in mammals. Follicular degeneration or atresia can occur at any stage of folliculogenesis during the estrous cycle to maintain ovarian homeostasis (7). The generally accepted mechanism is that elevated cortisol levels by various stressors trigger follicular atresia by interrupting steroid biosynthesis and maintenance of gonadotropin release (8, 9). These impaired conditions can cause irregular estrous cycles and anovulation in stressed females and mice (10). Generally, exposure to stress has a detrimental impact on reproductive potential, leading to a reduction in ovarian reserve.

However, the relationship between metabolic stress and ovarian reserve in women after severe physiological trauma has not been examined. In recent years, anti-müllerian hormone (AMH) is a glycoprotein secreted by granulosa cells of small growing follicles and has proven to be a more reliable clinical marker of ovarian reserve (11, 12).

This study analyzed whether metabolic stress was associated with serum AMH levels in women admitted to the intensive care unit.

MATERIAL and METHODs

Our aim in this study is to determine whether there is a relationship between metabolic stress and AMH in women hospitalized in Intensive Care Units, by comparing them with the control group. For this purpose, 37 women who were followed up in the Intensive Care Units of Siirt Training and Research Hospital between November 2022 and February 2023 were included in the study. The same number (n:37) was compared with the control group consisting of fertile healthy women who had regular menstruation, were at the same age and parity as the patient group, had no ovarian pathology, and excluded the variables affecting the AMH level. The institutional ethics committee approved the study with the number "2022/11/01/01".

Patients in the ICU were included in the study based on acute physiology and chronic health assessment (APACHI II) and injury severity score (ISS) score.(13) AMH, FSH, LH, E2, TSH, T3, T4, prolactin, CRP, cortisol, ACTH levels were analyzed from plasma samples taken at 8 am on the 5th day of hospitalization of both groups. The population of our study was female patients hospitalized in intensive care units. (n: 400) p: 2.66% and the confidence interval was 95%.The power (1-β) and margin of error (α) were determined for our study by calculating the sample size, and the power was planned to be at least 95% = DEFF*Np(1-p)]/ [(d2 /Z21-α/2*(N-1)+p*(1-p)].The sample size was calculated as 37.

Women over 18 and under 50 were included in both groups. Patients with premature ovarian failure, history of infertility, using oral contraceptives, previous ovarian surgery, taking chemotherapy drugs, smoking, political ovarian syndrome and obesity were excluded from the study.

Statistical Analysis: Statistical analyzes were performed with IBM® SPSS® 26 (SPSS Inc., Chicago, IL, USA). The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). For continuous data, Descriptive analyses were given as mean±standard deviation and median, min-max. Descriptive statistics were made by giving frequency and percentage values of categorical variables obtained from sociodemographic and clinical information. In continuous data (biochemical parameters etc.), student t-test was used for independent groups when it showed normal distribution, and Mann-Whitney U test was used when there was non-parametric distribution to compare binary groups (ICU vs. control). Receiver Operating Characteristic (ROC) and Youden's J analysis was used to determine index cut-off value. A p-value below 0.05 was considered statistically significant.

RESULTs

There was no significant difference in mean age between intensive care patients (29.3±8.3 , n=37) and control group (28.0±0.0 ,n=37) (p=0.349). A statistically significant difference was found between the AMH values between the patients hospitalized in the intensive care unit due to any operation and the control group (p=0.012). ICU hospitalized AMH values were significantly lower. On the other hand, while the T3 value was found to be significantly lower than that of the ICU control group (p < 0.0001), prolactin, CRP, and cortisol values were observed to be statistically higher.

In Table 2, the predictive properties of the parameters developing due to stress in the ICU were examined. Accordingly, when the AMH parameter drops below 1.74 units, it becomes a statistically significant predictive parameter, with a sensitivity of 59.5% and specificity of 70.3%, effectively distinguishing between ICU inpatients and control patients. In T3, 73.0% sensitivity and 86.5% specificity below 3.05 show predictive properties.

Prolactin, CRP and cortisol parameters show a significant predictive feature as the cut-off values of 11.15, 5.00 and 10.15 are exceeded, respectively.

**Table 1.** Comparison of biochemical parameters between groups

Variables	ICU patients (n=37)		Control group (n=37)		p Value
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
AMH	2,8±3,7	1,4(0,02-16,0)	3,4±2,4	2,9(0,4-10,4)	*0,012*
FSH	3,9±3,0	2,9(0,2-13)	4,6±2,7	4,0(1,0-12,0)	0,141
LH	4,9±4,2	4,0(0,1-17,0)	7,9±9,8	5,0(1,0-45,0)	0,108
E2	76,1±66,4	54,0(11,8-262,0)	69,9±57,0	49,0(12,0-266,0)	0,850
TSH	1,7±1,6	1,1(0,1-6,6)	1,8±1,4	1,3(0,3-6,2)	0,548
T3	2,7±0,5	2,6(1,3-3,8)	3,3±0,2	3,2(2,7-3,7)	*<0,0001**
T4	1,1±0,3	1,1(0,5-1,7)	1,1±0,1	1,0(0,9-1,3)	0,071*
Prolactin	23,1±35,6	16,0(4,3-226,0)	11,5±10,9	9,0(5,0-70,5)	*<0,0001*
CRP	71,9±59,4	48,0(2,0-171,0)	3,8±3,4	3,0(1,0-18,0)	*<0,0001*
Cortizol	16,4±12,9	13,5(1,7-69,0)	10,0±4,5	9,5(4,0-21,0)	*0,012*
ACTH	11,7±13,2	6,4(5,0-62,1)	9,1±6,2	6,8(5,0-36,8)	0,986

Anti-müllerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), adrenocorticotropic hormone (ACTH), cortisol. , prolactin , C-reactive hormone (CRP). For comparisons between groups, Mann-Whitney U test in non-parametric conditions and Student's t-test in parametric conditions were used. p<0.05 is statistically significant.

Table 2. Predictive properties of stress-related parameters in ICU patients; ROC Analysis

Variables	AUC	Std. Error	p value	Asymptotic 95% CI Lower Bound	Upper Bound	Sensitivity (%)	Specificity (%)	Cut-off Value
AMH	0,671	0,064	*0,012*	0,204	0,455	59,5	70,3	1,74
T3	0,854	0,046	*<0,0001*	0,055	0,237	73,0	86,5	3,05
Prolactin	0,764	0,056	*<0,0001*	0,654	0,874	67,6	73,0	11,15
CRP	0,920	0,035	*<0,0001*	0,853	0,988	89,2	86,5	5,00
Cortizol	0,671	0,065	*0,012*	0,544	0,797	70,3	59,5	10,15

Anti-müllerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), adrenocorticotropic hormone (ACTH), cortisol. , prolactin , C-reactive hormone (CRP).ROC analysis was performed and p<0.05 is significant.AUC; Area under curve, CI; Confidence Interval
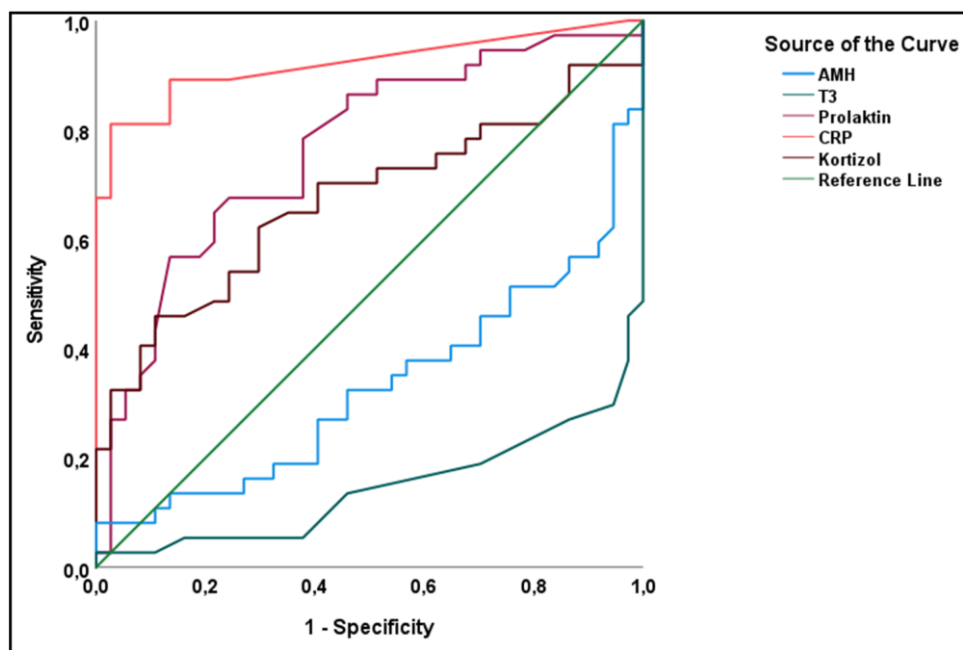
Figure 1. Predictive properties of stress-related parameters in ICU patients

DISCUSSION

Studies have indicated that the degree of suppression of both the central and peripheral axis of the reproductive axis in acute diseases correlates with the severity of the disease. It is reported that this suppression is affected apart from other factors (eg, age, drugs, head trauma, liver failure, etc.) that are known to change the reproductive axis independent of critical illnesses. The findings also report a general endocrine response to acute illness involving several hormonal axes, graded according to disease severity. Our study found a statistically significant difference between the AMH values between the patients hospitalized in the intensive care unit and the control group (p=0.012). AMH values were significantly lower in ICU hospitalized patients.

Dong YZ et al, in a cross-sectional study involving 576 women in the association of psychological stress AMH, reported that high psychological stress was associated with decreased AMH level in infertile women. They reported that psychological stress can affect ovarian reserve.(15). In the Mínguez-Alarcón L et al. study involving 520 patients, higher stress scores were negatively associated with antral follicle counts and serum AMH levels. Women at the second and third levels of stress scores also reported having lower mean serum AMH compared to women at the lowest levels. (16) In the study of 24 women in which, they investigated the associations between perceived stress, biomarkers of hypothalamic-pituitary-adrenal (HPA) activity, gonadotropin levels, and anti-Müllerian hormone (AMH) in women who have survived childhood cancer, the authors also found an inverse relationship between perceived stress and ovarian function. And found a positive correlation between HPA activity and ovarian function biomarkers (17).

According to Gao et al. They noted that after 8 weeks of chronic stress exposure, the number of primordial and preantral follicles and corpus luteum were significantly reduced in mice. In addition, model mice displayed elevated serum levels of follicle-stimulating hormone and corticosterone, along with reduced levels of luteinizing hormone, estradiol, testosterone, and anti-Müllerian hormone when compared to control mice (18).

Experimental research shows that prenatal stress affects reproductive function in female offspring, but human evidence is sparse and inconsistent. Bräuner et al. noted that maternal psychological stress in late pregnancy was associated with significantly higher uterine volume and ovarian antral follicle count (AFC) in adolescent offspring, but did not affect ovarian antimullerian hormone (AMH) or Inhibin B production (19).

In our study, T3 value was found to be significantly lower in ICU patients compared to the control group (p<0.0001), while prolactin, CRP, and cortisol values were found to be statistically higher. The cause of the changes remains unclear but may have been influenced by the close relationship between thyroid hormones, catecholamines and cortisol. Exogenous steroids suppress T3, so post-operative hypercortisolemia may also suppress T3 concentrations (20).

In our study, prolactin, CRP and cortisol parameters show a significant predictive feature as the cut-off values of 11.15, 5.00 and 10.15 are exceeded, respectively. Cortisol, CRP increases were negatively correlated with AMH.

Mitchell JM et al. In a study in which they examined the relationship between body mass index (BMI) and lifestyle factors such as smoking, alcohol intake, nutrition, exercise and stress, it was not found to be associated with AMH levels in women.(21) Shalom-Paz E et al. In their rat study, the researchers indicated that chronic maternal inflammation resulted in intrauterine growth restriction in offspring and led to decreased AMH levels due to follicular apoptosis (22).

Davidson et al., in their study involving female firefighters, also investigated the potential negative impacts of occupational exposure on the reproductive system in women with extensive work experience. Firefighter women had lower levels of AMH than non-firefighters. They noted that more research is needed to understand the mechanisms by which firefighting can reduce AMH and affect fertility (23). Women with POI had continuous exposure to adverse life events related to work stress, family stress, and trouble sleeping (24).

The limitations of our study are that our study includes the acute period of physiological stress, does not examine the long-term results, and cannot categorize patient groups. However, its strengths are that it is the first study to examine the effects of physiological stress on the reproductive system.

CONCLUSION

The majority of women express apprehension regarding the reproductive implications of past physiological stress. These patients often grapple with confusion and a lack of awareness about the repercussions of negative experiences on their reproductive system post-discharge and recovery. Our study serves to partially address the information gap in this area. The findings from my research demonstrate a reduction in AMH levels among ICU patients. Additionally, there is a correlated decline in AMH levels as cortisol levels increase. Consequently, it becomes evident that this circumstance has detrimental effects on ovarian reserves in women subjected to acute trauma.

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