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Copeptin: A potential marker for the prediction of poor ovarian reserve in the ınfertile women

Copeptin: İnfertil kadınlarda kötü over rezervinin ön görülmesinde potansiyel marker

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Abstract

Objective: There is actually no evidence regarding the physiological effects of copeptin in infertile women with different ovarian reserve types. This study aimed to investigate the relationship of serum copeptin level with poor ovarian reserve (POR) and to reveal the predictive value of copeptin for POR development in the infertile women.

Materials and Methods: All participant women were classified as the control group (n=77) included the women with diagnosis of unexplained infertility and the POR group (n=61) was composed of the women who met the European Society of Human Reproduction and Embryology consensus on POR [serum anti-Müllerian hormone (AMH) concentrations below 1.1 ng/mL]. The biochemical tests, including estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone, AMH and copeptin were analysed. The analyses of serum copeptin concentrations were measured by the means of competitive enzyme immunoassay.

Results: A significant increase in the serum copeptin level existed only in the POR group. There was a significant positive correlation between serum copeptin with E2 and FSH levels in the POR group. Significant negative correlations between copeptin and AMH concentrations (r=-0.310, p=0.015) and between copeptin concentration and antral follicle counts (r=-0.284, p=0.027) were detected only in the POR group. The estimated areas under receiver operating characteristic curves for serum concentration were found to be statistically significant with a cut-off value of 3.52 (95% confidence interval 0.519-0.709), sensitivity 0.90 and specificity 0.72.

Conclusion: This study confirmed that there was an elevated serum copeptin concentration in the infertile women with POR and that serum copeptin concentration may have a predictive value for POR diagnosis.

Keywords: Copeptin, infertility, poor ovarian reserve, vasopressin

Öz

Amaç: Farklı over rezerv tiplerine sahip infertil kadınlarda kopeptinin fizyolojik etkilerine dair aslında yeterli kanıt yoktur. Bu çalışmanın amacı, infertil kadınlarda serum kopeptin düzeyi ile zayıf over rezervi (POR) arasındaki ilişkiyi araştırmak ve kopeptinin POR gelişimi için prediktif değerini ortaya çıkarmaktır.

Gereç ve Yöntemler: Katılımcılar, açıklanamayan infertilite tanılı kadınları içeren kontrol grubu (n=77) ve POR grubu (n=61), olarak sınıflandırıldı. POR tanı grubu Avrupa İnsan Üremesi ve Embriyoloji Derneği kriterlerini karşılayan kadınlardan oluşturuldu [serum anti-Müllerian hormon (AMH) konsantrasyonları 1,1 ng/mL altındadır]. Estradiol (E2), folikül uyarıcı hormon (FSH), luteinize edici hormon, AMH ve kopeptin içeren biyokimyasal testler analiz edildi. Serum kopeptin konsantrasyonlarının analizleri, enzim immünoassay vasıtasıyla ölçüldü.

Bulgular: Serum kopeptin düzeyinde anlamlı artış POR grubunda mevcuttu. POR grubunda serum kopeptin ile E2 ve FSH seviyeleri arasında anlamlı pozitif korelasyon vardı. Kopeptin ve AMH konsantrasyonları (r=-0,310, p=0,015) ve kopeptin konsantrasyonu ile antral folikül sayısı (r=-0,284, p=0,027) arasında anlamlı negatif korelasyonlar POR grubunda saptandı. Serum konsantrasyonu için alıcı işletim karakteristiği eğrileri altındaki tahmini alanların, kesme değeri 3,52 (%95 güven aralığı 0,519-0,709), duyarlılık 0,90 ve özgüllük 0,72 ile istatistiksel olarak anlamlı olduğu bulundu.

PRECIS: We investigated the relationship of serum copeptin level with poor ovarian reserve (POR) and to reveal the predictive value of copeptin for POR development in the infertile women.

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Sonuç: Bu çalışma, POR grubundaki infertil kadınlarda serum kopeptin konsantrasyonunun yükseldiğini ve serum kopeptin konsantrasyonunun POR tanısı için öngörücü bir değere sahip olabileceğini doğruladı.

Anahtar Kelimeler: Copeptin, infertilite, kötü over rezervi, vazopressin

Introduction

The term "ovarian reserve" is traditionally described as a female's reproductive potential specifically in the sense of the number and content of oocytes in the ovaries[1]. The etiopathogenesis of poor ovarian reserve (POR) has not clearly documented as yet. However, many etiologies, including age-related decline in ovarian follicles, severe endometriosis, chromosomal and genetic disorders, prior pelvic surgery, metabolic, autoimmune and infectious diseases, as well as exposure to toxic agents were identified[2-4]. In the existing literature, the POR prevalence was estimated as 6-35%[5,6]. This huge discrepancy presumably arises from the absence of conclusive collectivity in the POR definition.

On the purpose of POR terminology, a European Society of Human Reproduction and Embryology Working Group reported a consensus termed as Bologna criteria[7]. Despite the Bologna criteria exhibiting unsatisfactory uniformity in the POR definition, most scientific authorities have recently accepted these criteria. Despite the considerable progress in modern assisted reproduction technology in the last 40 years, the clinical management of infertile women with POR is still a challenge in clinical practice. Consequently, this may lead to great disappointment and discouragement for the patients and clinicians.

Copeptin possesses a molecular structure of glycosylated 39-amino-acid peptide, which is a C-terminal part of pre-provasopressin (preproAVP). PreproAVP is an initial protein containing a signal peptide, arginine vasopressin (AVP), neurophysin II and copeptin[8,9]. During the transport from the hypothalamus to posterior hypophysis, copeptin and neurophysin II mainly participate as carrier proteins of AVP. All these molecules are cleavage products in their course in the pituitary gland and are concurrently secreted into the bloodstream. The main physiological actions of AVP are the homeostasis of fluid balance, the maintenance of vascular tonus and regulation of the endocrine stress response. The AVP receptors exist in many organs and tissues, including the kidney, liver, vascular smooth muscles, and brain[10]. However, the exact role of copeptin in the circulation is not clearly elucidated for this moment[11,12]. Copeptin is simultaneously synthesized with AVP and detected at equimolar concentrations[12]. Therefore, copeptin level confidentially reflects equivalent AVP concentration in the circulation.

In the present studies, copeptin emerged as a new diagnostic and prognostic marker in various diseases, including diabetes insipidus, diabetes mellitus, sepsis, pneumonia, chronic obstructive pulmonary disease, heart failure and myocardial infarction[13]. However, in the accumulated literature, no evidence regarding the physiological effects of copeptin actually exists in infertile women with POR. Hence, this study aimed to investigate the relationship between serum copeptin level and POR status and to reveal the predictive value of copeptin for POR development in infertile women.

Materials and Methods

Setting

This analysis was performed in a prospective observational (cross-sectional) manner in the Department of Reproductive Endocrinology between January 2021 and June 2021. The approval of this study approved by the Ethics Committee of the University (reference number: 386/2021) compatible with the Declaration of Helsinki. Written informed consent was collected from all participant women before the study.

Study Population

During the first visit, the detailed medical characteristics were recorded for all volunteers. Infertile women with prior pelvic surgery, endometriosis, adnexal masses, chemotherapy, radiotherapy, smoking, body mass index (BMI) ≥30 kg/m^2, systemic diseases, and medications affecting adversely fertility capacity were excluded from the study. During clinical evaluation, the total antral follicle counts (AFC) were calculated in the early follicular phase of the menstrual cycle by the means of a transvaginal 7.5 MHz probe (Toshiba Xario 100, Toshiba Medical System Co., Nasu, Japan). Eventually, the infertile women aged 20 to 40 years and who met the eligibility criteria were enrolled in this study.

Unexplained infertility is described as the lack of a definable cause to achieve a pregnancy after 12 months of attempting conception despite a thorough evaluation[1]. In the Bologna consensus on the definition of poor response, at least two of the following three criteria had to be present to establish the definition[7]:

(1) Advanced maternal age (>40 years) or any other risk factor for POR.

(2) A previous POR (≤3 oocytes with a conventional stimulation protocol).

(3) An abnormal ovarian reserve test [i.e. AFC less than 5-7 follicles or anti-Müllerian hormone (AMH) below 0.5-1.1 ng/mL].

The study groups were recruited from the infertile women who planned to receive the first in vitro fertilization therapy. All participant women (n=138) were classified as two study groups based on the ovarian reserve patterns. While the control group (n=77) included the women with a diagnosis of unexplained infertility, the POR group (n=61) was arose from the women who had serum AMH concentrations below 1.1 ng/mL as

indicated in the items of Bologna criteria for abnormal ovarian reserve test.

Biochemical Evaluations

After overnight fasting, the venous samples were drawn from the antecubital veins and collected in 5 mL seperator tubes (BD Vacutainer, Becton Dickinson, New Jersey, USA) in the early follicular phases of the menstrual cycle on day 2 to 4. The laboratory workers who studied the samples were unaware of the study groups. The blood samples for hormonal measurements were centrifuged for 20 min at 1,000 x g. The serum levels of estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH) were measured using an electrochemiluminescence immunoassay (ECLIA) method by an autoanalyser (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany).

The sera for copeptin and AMH analyses were drained into cryo tubes to be stored at -80 °C until the day of analysis. The serum concentrations of AMH were evaluated by the ECLIA method using an autoanalyser (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany). The analyses of serum copeptin concentrations were measured by the means of competitive enzyme immunoassay (Human Vasopressin-neurophysin 2-copeptin ELISA kit: EIAab Wuhan EIAab Science Co. Ltd.; East Lake Hi-Tech Development Zone, Wuhan 430079, China).

Sample Size Estimation and Matching Analysis

Priori power analysis was performed for the Students' t-test when the study was designed. To specify the sample size, the Cohen effect size was estimated with aids of literature information[14]. For two-side minimum 95% power hypothesis, 0.05 margin of error, and 0.8 effect size; a minimum number of 35 participants for both the control and the study groups were, respectively, estimated. Matching analysis based on propensity score match was performed by the means of R studio software (Version 1.2.5042, R Core Team, Vienna, Austria) to eliminate the age- effect on data. To match cases and controls for the confounding variables of age, the MatchIt library 3.0.1 in the R package was used.

Statistical Analysis

All statistical the data were analyzed with SPSS (Statistical Packages for The Social Sciences) software version 21 (SPSS Inc. Chicago, IL, USA). The normality pattern of statistical distribution was evaluated by Shapiro-Wilk test. For comparisons of the study groups, the Student's t-test and the Mann-Whitney U test for normally and non-normally distributed data were, respectively, used. The descriptive statistics are given as mean (± standard deviation) and median (min-max) according to distribution patterns. The correlation analysis between the copeptin and other study parameters was assessed by Pearson's correlation test. To determine the discriminant power of the index (maximum sensitivity and selectivity) using the receiver operating characteristic (ROC) analysis method, the ROC graphs were drawn, the area under the curve with 95% confidence intervals were estimated. The Youden index was used to determine the best cut-off point in ROC analysis with sensitivity and specificity values for predicting POR development. The statistical significance level was considered $p<0.05$.

Results

We studied 138 participant women as the study population. The comparisons of clinical and biochemical characteristics are exhibited in Table 1. The means of age and BMI values were statistically comparable for the control and POR groups ($p=0.121$ and $p=0.749$, respectively). The E2, FSH, and LH concentrations were elevated in the infertile women with POR compared with the control group ($p<0.05$, for all). Unsurprisingly, the serum levels of AFC and AMH were significantly decreased in the POR group ($p<0.001$, for both). Additionally, a significant rise in the serum copeptin level existed only in the POR group ($p=0.022$).

The correlation analysis of serum copeptin level with other study parameters can be viewed in Table 2. The Pearson's analysis demonstrated that the mean ages of the participant women in the control and POR groups did not exhibit any correlation with serum copeptin level. The BMI value of the control group showed a statistically significant positive correlation ($r=0.359$, $p<0.001$). There was a significant positive correlation between

Table 1. Comparisons of clinical and biochemical characteristics of the study parameters

	Control group (n=77) Mean ± standard Median (min-max)	POR group (n=61) Mean ± standard Median (min-max)	p
Age (years)	30.2±4.8 30 (20-40)	31.4±3.7 32 (23-39)	0.121
BMI (kg/m²)	22.5±2.4 22.1 (17.1-29.1)	22.9±3.03 21.8 (17.5-29.4)	0.749
E2 (pg/mL)	77.1±11.2 77.6 (51.0-105.5)	80.3±16.6 83.9 (22.3-122.2)	0.021*
FSH (IU/L)	5.5±1.3 5.4 (2.4-9.6)	8.5±3.3 8.7 (3.4-20.4)	<0.001*
LH (IU/L)	5.5±1.4 5.7 (3.2-9.1)	7.8±2.9 7.3 (3.5-13.8)	<0.001*
AMH (ng/dL)	5.6±1.9 5.8 (1.5-9.6)	0.8±0.2 0.7 (0.5-1.0)	<0.001*
AFC	14.2±4.6 13 (4-24)	5.5±2.3 5 (1-10)	<0.001*
Copeptin (ng/mL)	4.2±0.9 4.3 (2.2-6.6)	5.1±1.7 4.4 (2.0-9.8)	0.022*

POR: Poor ovarian reserve, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, AMH: Anti-Müllerian hormone, AFC: Antral follicle count, min-max: Minimum-maximum, *p-values <0.05 are accepted as statistically significant

serum copeptin E2 level (r=0.434, p<0.001) and a significant positive correlation FSH level (r=0.328, p=0.01) in the POR group. However, no statistically significant correlation was observed between LH and copeptin existed in both study groups. A significant and negative correlation between AMH and copeptin (r=-0.310, p=0.015) was detected only in the POR group. Also, a significant and negative correlation between copeptin concentration and AFC existed in the POR group (r=-0.284, p=0.027).

Table 3 describes the serum copeptin concentration in predicting the POR development. The estimated areas under ROC curves for serum concentration were found to be statistically significant (p=0.022) with a cut-off value of 3.52 (95% confidence interval 0.519-0.709), sensitivity 0.90 and specificity 0.72.

Discussion

This study focused on investigating the relationship between serum copeptin level and POR status and ascertaining the predictive value of copeptin for POR development. Consequently, an increased serum copeptin level was found in the infertile women with POR diagnosis. Additionally, the serum copeptin level may predict the POR diagnosis in the study population.

Copeptin (also known as AVP-associated glycoprotein) was firstly identified in 1972 by Hanaoka and Guggino[15]. Because of the stoichiometric production with AVP, copeptin was accepted as a reflection of serum AVP concentration. The plasma AVP measurements are a great challenge because AVP is a small molecular size and shows more avidity to platelets[16]. Additionally, AVP exhibited an unstable state even when stored at -20 °C due to short- life time of AVP (about 24 min)[11,17]. All these reasons contribute to the lack of routine clinical practice of AVP. Since Morgenthaler et al.[18] defined an assay technique for copeptin, it became a preferred choice for investigators to reveal the functions of AVP.

Table 2. Correlation analysis of serum copeptin concentration with other study parameters

	Control group (n=77)		POR group (n=61)	
	r	p	r	p
Age (years)	0.106	0.359	-0.232	0.071
BMI (kg/m²)	0.359	0.001*	0.161	0.216
E2 (pg/mL)	0.026	0.823	0.434	<0.001*
FSH (IU/L)	0.001	0.995	0.328	0.01*
LH (IU/L)	-0.025	0.829	-0.235	0.068
AMH (ng/dL)	0.326	0.051	-0.31	0.015*
AFC	0.080	0.457	-0.284	0.027*

POR: Poor ovarian reserve, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizicng hormone, AMH: Anti-Müllerian hormone, AFC: Antral follicle count, *p-values <0.05 are accepted as statistically significant

Unlike AVP, copeptin keeps stability in EDTA plasma for up to 2 weeks at room temperature[19]. In a large study by Roussell et al.[20], the authors compared the copeptin and AVP concentrations and noticed a strong correlation between the serum copeptin and AVP levels. There are four main advantages of serum copeptin measurements to AVP; (i) less sample size (ii) no extraction procedure (iii) less time to analyse and (iv) more sensitivity. Based on these facts, serum routine measurements of copeptin have become a rational reason for preference for the investigators.

The physiological role of copeptin is not elucidated at present. Prior studies reported conflicting findings regarding the physiological roles of copeptin[21,22]. In the recent studies, copeptin was professed to be a chaperone-like molecule related to the structural formation of propre AVP[23]. Despite the lack of strong evidence in the current literature, copeptin itself may have specific peripheral functions, Substantially, copeptin shows a rapid response to osmotic, hemodynamic and unspecified stress-related stimuli as occurred in AVP.

A normal range of copeptin concentration, the median plasma concentration was detected in healthy people to be 4.2 pmol/L with a wide range between 1 and 13.8 pmol/L[18,24]. Women had slightly lower values than men with a difference of only 1 pmol/L[18,24]. Copeptin concentrations did not correlate with age[18] and circadian variability[25]. Copeptin secretion appeared not to be influenced by food intake[26] and menstrual cycle in women[27]. Additionally, fasting and exercise induced an increase in copeptin concentration[28]. Based on these facts, copeptin measurements can be confidentially evaluated independently of withdrawal time, prandial state, or menstrual cycle phases.

A hallmark of stress response is the activation of the hypothamo-pituitary-adrenal axis[29]. Hormonal cascades induce the secretion of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothamus. AVP is another hypothalamic hormone stimulated by different stress

Table 3. Serum copeptin concentration in predicting the POR development

Copeptin (ng/mL)	
AUC (95% CI)	0.614 (0.519-0.709)
Cut-off	3.52
Sensitivity	0.90 (0.79-0.95)
Specificity	0.72 (0.61-0.81)
PPV	0.72 (0.60-0. 0.81)
NPV	0.90 (0.79-0.96)
LR+	1.23 (1.02-3.78)
p-value	0.022*

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likehood ratio, POR: Poor ovarian reserve, CI: Confidence interval, *p-values <0.05 are accepted as statistically significant

stimuli. This seems to have a potentiating effect on CRH. Eventually, these two hormones are the main inducers of adrenocorticotropic hormone[30-33]. The duration of stressor exposure (acute vs chronic), the type of stressor (physical vs pychological), age and gender have effects on the pattern and magnititude of response to stressor. In addition to hemodynamic and osmoregulatory effects, AVP may be considered a reflection of the increased stress and inflamation[9,33]. Moreover, copeptin was demonstrated to be favorable in reflecting individual stress level due to its relatively stable serum concentration.

In this study, we demonstrated that there was a significant increase in serum copeptin concentration and significant correlations between serum copeptin level and ovarian reserve markers, including E2, FSH, AFC, and AMH, only in infertile women with POR. At this stage, it can be hypothesized that the POR status in infertile women may have received a stress stimulus by the hypothalamus. Subsequently, this stimulus may induce an increased AVP and copeptin release into the bloodstream. Therefore, serum copeptin levels may be used as a predictive marker of POR development in infertile women.

As far as we know, this study is the preliminary study revealing the relationship between serum copeptin levels with different ovarian reserve patterns. This issue can be considered the main strength of this study.

Study Limitations

The limitation of the study is that we could not investigate the stress hormone levels such as CRL, ACTH, or cortisol in the study groups.

Conclusion

In summary, this study confirmed that that there was an elevated serum copeptin concentration in the infertile women with POR and that copeptin might have a predictive value for the POR development. Future large-sized prospective studies are required to clarify the potential effects of copeptin in the POR pathogenesis.

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Ethics

Ethics Committee Approval: The approval of this study approved by the Ethics Committee of the Hitit University (reference number: 386/2021) compatible with the Declaration of Helsinki.

Informed Consent: Written informed consent was collected from all participant women before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y., Concept: E.Y., Design: E.Y., Data Collection or Processing: E.Y., Analysis or Interpretation: E.Y., Literature Search: E.Y., Writing: Ü.G., E.Y.

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