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The Relationship between Anti-mullerian Hormone and Prolactin Levels in Polycystic Ovarian Syndrome

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ABSTRACT

Objectives: This study aimed to investigate serum anti-Mullerian hormone (AMH) and prolactin levels in polycystic ovarian syndrome (PCOS) according to the presence of oligomenorrhea.

Methods: Women with PCOS who were admitted to an endocrinology outpatient clinic consecutively between January and December 2020 were enrolled in this study retrospectively. The age of the patients included in this study was between 18 and 40 years. Patients diagnosed with PCOS according to Rotterdam revised criteria. Demographic and clinical characteristics of the patients were obtained from patients' files.

Results: A total of 301 women with PCOS were enrolled in this study. The mean prolactin levels were 20.0±8.5 ng/mL and 22.2±5.5 ng/mL in PCOS patients with and without oligomenorrhea (p=0.091). No significant differences in AMH levels were also found between the two groups 5.3 (5.2–5.4) versus 5.3 3 (5.0–6.0) ng/mL, respectively (p=0.798). AMH levels were positively correlated with prolactin and negatively with follicular-stimulating hormone in PCOS subjects (r=0.512, p<0.001, r=–0.155, p=0.007, respectively). The oligomenorrhea group demonstrated increased serum glucose and Vitamin D levels and platelet distribution width value and decreased glycated hemoglobin, estradiol, free testosterone, hemoglobin, and red cell distribution width values (p<0.001, p=0.017, p=0.018, p=0.001, p=0.008, p=0.027, p=0.001, and p=0.010, respectively). In addition, serum prolactin had a relationship between free testosterone and vitamin D levels (r=0.210, p<0.001; r=–0.123, p=0.320, respectively).

Conclusion: AMH and prolactin levels did not differ in PCOS patients with and without oligomenorrhea.

Keywords: Anti-Mullerian hormone, oligomenorrhea, polycystic ovary syndrome, prolactin

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among reproductive-age women leading to the major cause of infertility and is characterized by hyperandrogenism and menstrual irregularities such as oligomenorrhea, chronic anovulation, and polycystic ovarian morphology.[1] PCOS is closely associated with metabolic abnormalities, including abdominal obesity, dyslipidemia, and insulin resistance (IR), and may lead to an increased incidence of long-term risk of metabolic syndrome, diabetes mellitus, cardiovascular diseases, and infertility. The underlying involvement of biological mechanisms in these abnormalities still remains complex and inconclusive.[2] Identification of potential molecular pathogenic mechanisms and interacting processes that contribute to the pathogenesis of PCOS provide additional data for the development of a diagnostic and therapeutic target in the management of metabolic alterations in PCOS patients.

Prolactin is a multifunctional pleiotropic polypeptide secreted mainly by the lactotrophs of the anterior pituitary gland and also extra pituitary tissues such as the endometrium, decidua, breast, adipose tissue, and brain that is involved in numerous physiological and pathophysiological processes including lactation, appetite, homeostasis, immunity, tumorigenesis, luteal function, and reproduction.[3] In recent years, prolactin has been shown to be a potent diabetogenic and lipogenic factor that affects glucose and lipid metabolisms and insulin functions of pancreatic beta cells and adipose tissues.[4] Some studies have reported that prolactin secretion may be impaired in PCOS, but the mechanism involved has not been fully defined.[5,6]

Anti-Mullerian hormone (AMH) is a glycoprotein hormone from the transforming growth factor-β family. It is secreted from granulosa cells within pre-antral and small antral follicles in the ovaries to regulate folliculogenesis.[7] Its level peaks with puberty and gradually declines with age until it becomes undetectable at the post-menopausal period, and it is tightly related to the number of antral follicles in both healthy individuals and PCOS patients, suggesting that AMH is an indirect biomarker of the ovarian follicular reserve.[7,8] Previous studies have reported that hyperandrogenism, altered glucose metabolism and insulin sensitivity, and increased body mass index (BMI) are associated with elevated AMH levels in PCOS women.[9] However, the relationship between serum AMH and prolactin levels on the pathogenesis of PCOS has not been comprehensively investigated yet.

This study aimed to assess serum AMH and prolactin levels between biochemical features in PCOS according to the presence of oligomenorrhea.

METHOD

This retrospective study was carried out in Prof. Dr. Süleyman Yalçın City Hospital, Department of Endocrinology, between January and December 2020 in patients 18 and 40 years old. Based on the American Society for Reproductive Medicine Rotterdam Revised Diagnostic Criteria, 301 patients diagnosed with PCOS were included in the study.[10] The patients included in the study were divided into two groups: oligomenorrheic and non-oligomenorrheic. A patient can be diagnosed with PCOS based on the Rotterdam criteria when two of the following three criteria are present: (1) Biochemical and/or clinical signs or symptoms associated with excess androgen activity, (2) oligo ovulation or anovulation, and (3) the presence of ≥12 follicles with a diameter of 2–9 mm or ovarian volume of >10 mL (without a cyst or dominant follicle in either ovary) upon gynecologic ultrasonography imaging examination. In addition, the following exclusion criteria were also considered: Irregular menstrual cycles and/or androgen excess, including congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, and hyperprolactinemia. Patients with thyroid conditions, cardiovascular diseases, autoimmune disorders, chronic inflammation, acute or chronic infections, breastfeeding and pregnancy, systemic diseases that could alter insulin sensitivity, such as diabetes mellitus, gestational diabetes mellitus, and impaired glucose tolerance, malignancy, hypertension, smoking, or excessive alcohol consumption were excluded from the study. Patients who received any medication that could alter insulin sensitivity, prolactin levels, or sex steroid levels within the past 6 months were also excluded from the study. All participants' prolactin levels were within the normal range; serum prolactin levels above 25 ng/mL were considered hyperprolactinemia.

Demographic and clinical characteristics of the patients recruited to study, including age, BMI, the anamnesis of oligomenorrhea, and infertility, were obtained from patients' files. The BMI of all participants was calculated as body weight (kilograms) divided by the square of body height (meters). Hirsutism scoring was done subjectively with the Ferriman–Gallwey (FG) score by the same physicians from the research team. The distribution of terminal hair in 11 androgen-sensitive areas was scored from 0 (no terminal hair) to 4 (severe hirsutism). The total score was found by summing the scores from all areas, indicating no hair growth (0 points), mild (1–7 points), moderate (8–15 points), or severe (≥15 points). Hirsutism was evaluated by the same physician and determined by a total FG score of ≥8. Ultrasonographical evaluation and measurements of all participants were performed by the same researcher.

Biochemical tests were performed from venous blood samples after overnight fasting during the early follicular phase (on days 3–5 of the natural menstrual cycle) or with progesterone-withdrawal bleeding if the patient had amenorrhea. Blood samples were kept at room temperature for 30 min after collection and centrifuged at 2000 g for 15 min to obtain serum. Complete blood count, including white blood count, platelet count, hemoglobin value, red cell distribution width (RDW), platelet distribution width (PDW), and mean platelet volume, was measured using Mindray BC-6800 autoanalyzer (Mindray Electronics Co, Ltd, Shenzhen, China). Serum glucose and glycated hemoglobin (HbA1c) levels were determined by photometric method with an Olympus AU 2700 autoanalyzer (Beckman Coulter Inc., CA, USA). Serum follicular-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid-stimulating hormone, free thyroxine (T4), Vitamin B12, Vitamin D, in-

sulin, and prolactin levels were measured using chemiluminescent enzyme immunoassay on the UniCel DxI 800 (Beckman Coulter Inc.). IR was assessed using the homeostatic model assessment of IR (HOMA-IR = fasting blood glucose (mg/dL) × fasting insulin (mIU/L)/405). Thyroid peroxidase antibodies and thyroglobulin antibodies were measured by a chemiluminescent immunometric assay using Roche Elecsys autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). Free testosterone, total testosterone, dehydroepiandrosterone sulfate, and 17-OH progesterone were determined by radioimmunoassay with Cobas E 601 (Roche Diagnostics GmbH). After the samples were collected in lithium heparin tubes, serum AMH levels were measured using an automated electrochemiluminescence immunosorbent assay using the Elecsys reagent kit on Cobas autoanalyzer (Roche Diagnostics GmbH) according to the manufacturer's instructions. The analytical sensitivity of this assay was 0.03 ng/mL, and the inter-and intra-assay coefficients of variations of this method were 3.7% and 2.1%, respectively.

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to determine whether variables are normally distributed. Data are given as mean±standard deviation or median (25^{th}–75^{th} percentile) for continuous variables according to the normality of distribution and as frequency, and percentage for categorical variables. Normally distributed variables were analyzed with independent samples t-test. Non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square or Fisher's exact tests. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Two-tailed $p<0.05$ were considered statistically significant.

RESULTS

A total of 301 patients with PCOS were recruited in the study. The mean age of patients was 29.5±4.6 years, and the mean BMI values were 25.9±3.5 kg/m^2. Out of these patients, 134 (44.5%) of them were normal, 121 (40.2%) were overweight, and 46 (15.3%) were obese. Results also revealed that 279 (92.7%) patients had oligomenorrhea, 219 (72.8%) women presented with hirsutism, and 85 (28.2%) with a history of infertility. Patients' clinical and biochemical features regarding the presence or absence of oligomenorrhea are summarized in Table 1.

There were no significant differences between the two groups in terms of the presence of hirsutism, the history of infertility, and ultrasonographic findings (p=0.888, p=0.072, p=1.000, respectively).

Serum AMH was positively correlated with serum prolactin levels in PCOS patients (r=0.512, p<0.001). The relationship between participants' characteristics and laboratory measurements and AMH and prolactin are summarized in Table 2.

DISCUSSION

The present study aimed to investigate relationships between AMH and prolactin levels and clinical and biochemical features in patients diagnosed with PCOS. There was no significant difference between AMH and prolactin levels in terms of oligomenorrhea in PCOS patients. In PCOS patients with oligomenorrhea, increased serum levels of glucose and vitamin D were observed, along with elevated PDW values. In addition, decreased levels of HbA1c, estradiol, free testosterone, hemoglobin, and RDW values were noted compared to those without oligomenorrhea. A positive correlation between AMH and prolactin levels was found, and a negative correlation between AMH and FSH was observed in PCOS subjects. It was also demonstrated that a relationship existed between serum prolactin, free testosterone, and Vitamin D levels.

Menstrual disorders, including oligomenorrhea and anovulation, and resulting infertility are clinical characteristics of PCOS and hyperprolactinemia.[11] For that reason, relationships between PCOS and hyperprolactinemia have been investigated in several studies. There is debate as to whether the similarities between PCOS and hyperprolactinemia are because they share a common pathophysiological mechanism, are coincidental, have a cause-effect relationship, or are both different clinical conditions. Forbes et al. demonstrated in six patients with prolactin adenoma related to clinical hyperandrogenism in 1954. Filho et al. showed that 16% of 82 PCOS women presented with elevated circulating prolactin levels; of them, nine had prolactin adenomas, three were associated with hyperprolactinemic drugs, and one had macroprolactin, suggesting that hyperprolactinemia is not a clinical PCOS manifestation.[12] Hassan et al. demonstrated in 53 infertile women that hyperprolactinemia is more frequent in PCOS patients than in non-PCOS patients.[13] Hayashida et al. revealed that prolactin levels increased in 5.8% of 259 patients diagnosed with PCOS, and they explained this by the presence of macro prolactin, which is in a biologically inactive form and causes falsely elevated measurements.[14] The researchers also found that PCOS patients with macro prolactin had lower BMI and HOMA-IR than women without macro prolactin. Szosland et al. showed a similar daily profile of prolactin levels in patients with PCOS than those without PCOS.[5] The causative relationship between PCOS and hyperprolactinemia has been investigated in previous studies. One opinion is based on elevated LH levels in patients with PCOS, which leads to a secondary decrease in dopaminer-

Table 1. Participants'' characteristics and laboratory measurements with regard to the presence of oligomenorrhea

	Total (n=301)	Oligomenorrhea		p
		Absent (n=22)	Present (n=279)	
Age (years)	29.5±4.6	31.1±4.6	29.4±4.6	0.090*
Body mass index (kg/m^2)	25.9±3.5	27.7±4.5	25.7±3.4	0.054*
AMH (ng/mL)	5.3 (5.0–6.0)	5.3 (5.2-5.4)	5.3 (5.0–6.0)	0.798†
Prolactin (ng/mL)	20.1±8.3	22.2±5.5	20.0±8.5	0.091*
Free T4 (ng/mL)	1.1 (0.9–1.3)	1.0 (0.9–1.1)	1.1 (0.9–1.3)	0.664†
TSH (mIU/mL)	1.7 (1.1–2.4)	1.2 (1.1–2.2)	1.7 (1.1–2.4)	0.210†
TPO-Ab positivity	124 (41.2)	7 (31.8)	117 (41.9)	0.482§
TG-Ab positivity	57 (18.9)	5 (22.7)	52 (18.6)	0.581§
HbA1c (%)	5.3±0.3	5.5±0.3	5.3±0.3	0.001*
Blood glucose (mg/dL)	89.1±6.2	85.6±3.3	89.4±6.3	<0.001*
Insulin (µIU/mL)	7.0±2.2	7.6±2.1	7.0±2.2	0.245*
HOMA-IR	1.6±0.5	1.6±0.4	1.6±0.5	0.675*
Vitamin D (ng/mL)	23.1 (15.4–32.0)	17.6 (13.5–24.3)	23.8 (16.0–32.0)	0.017†
Vitamin B12 (pg/mL)	322.0 (236.0–418.0)	321.5 (226.0–380.0)	322.0 (236.0–419.0)	0.697†
FSH (mIU/mL)	6.4±1.5	6.5±1.5	6.4±1.5	0.789*
LH (mIU/mL)	6.6 (5.4–8.2)	7.5 (5.3–9.0)	6.6 (5.4–8.2)	0.562†
Estradiol (pg/mL)	26.9 (23.6–36.5)	34.8 (29.0–41.0)	26.4 (23.5–36.5)	0.008†
17-OHPG (ng/mL)	0.9±0.3	0.9±0.2	0.9±0.3	0.309*
Total testosterone (ng/mL)	26.8±8.2	25.4±6.1	26.9±8.4	0.420*
Free testosterone (pg/mL)	0.8±0.3	1.0±0.3	0.8±0.3	0.027*
DHEA-S (µg/dL)	297.2±64.3	311.8±45.2	296.0±65.6	0.141*
Hirsutism	216 (71.8)	15 (68.2)	201 (72.0)	0.888§
Infertility	84 (27.9)	2 (9.1)	82 (29.4)	0.072#
USG findings	298 (99.0)	22 (100.0)	276 (98.9)	1.000#
WBC (10^9/L)	8.1±2.8	8.8±3.1	8.1±2.8	0.273*
Hemoglobin (g/dL)	12.7±1.3	13.2±0.7	12.7±1.3	0.001*
RDW (fL)	34.6 (32.4–40.9)	41.9 (32.6–43.8)	34.4 (32.4–39.6)	0.010†
Platelet count (10^9/L)	242.0 (196.0–278.0)	203.5 (139.0–289.0)	242.0 (199.0–278.0)	0.159†
MPV (fL)	9.5±1.3	9.3±0.8	9.5±1.4	0.337*
PDW (fL)	11.9 (10.3–17.3)	10.3 (10.0–12.6)	12.0 (10.4–17.6)	0.018†

AMH: Anti-Mullerian hormone; DHEA-S: Dehydroepiandrosterone sulfate; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment of insulin resistance; FSH: Follicular stimulating hormone; LH: Luteinizing hormone; MPV: Mean platelet volume; 17-OH PG: 17-hydroxy progesterone; PDW: Platelet distribution width; RDW: Red cell distribution width; T4: Free thyroxine; TSH: Thyroid stimulating hormone; TPO-Ab: Thyroid peroxidase antibodies; TG-Ab: Thyroglobulin antibodies; USG: Ultrasonography; WBC: White blood cell count.

Data are presented as mean±standard deviation, median (25th–75th percentile) and n (%).

*Student t test, †Mann-Whitey U test, §Chi-square test, #Fisher's exact test.

gic tone, resulting in elevated prolactin levels. Another hypothesis proposes that relative hyperestrogenemia in PCOS women induces elevated prolactin secretion and synthesis. Recently, Delcour et al. demonstrated no connection between hyperprolactinemia and PCOS in a review of the literature.[15] Consistently, similar prolactin levels were found in PCOS patients with oligomenorrhea as in those without oligomenorrhea. Our study indicates that impaired prolactin secretion and elevated circulating prolactin levels are not clinical manifestations of PCOS. In cases of oligomenorrheic patients with hyperprolactinemia, we recommend a comprehensive etiological investigation to explore the classical etiologies of hyperprolactinemia (drugs, stress, hypothyroidism, adenoma, chronic kidney failure, cirrhosis, etc.) before concluding that elevated circulating prolactin is secondary to PCOS.

Table 2. Relationship between participants' characteristics and laboratory measurements and AMH and prolactin

	AMH		Prolactin	
	r	p	r	p
Age (years)	–0.075	0.192†	0.014	0.804*
BMI (kg/m²)	0.084	0.147†	–0.040	0.485*
Free T4 (ng/mL)	0.079	0.174†	–0.007	0.909†
TSH (mIU/mL)	0.058	0.312†	0.063	0.278†
HbA1c (%)	0.004	0.948†	0.086	0.137*
Blood glucose (mg/dL)	–0.090	0.118†	–0.031	0.588*
Insulin (µIU/mL)	0.023	0.693†	0.084	0.146*
HOMA-IR	0.001	0.992†	0.071	0.220*
Vitamin D (ng/mL)	–0.008	0.886†	–0.123	0.032†
Vitamin B12 (pg/mL)	–0.055	0.343†	0.087	0.130†
FSH (mIU/mL)	–0.155	0.007†	–0.093	0.107*
LH (mIU/mL)	–0.109	0.059†	–0.004	0.945†
Estradiol (pg/mL)	–0.099	0.088†	–0.012	0.836†
17-OHP(ng/mL)	–0.046	0.424†	–0.013	0.827*
Total testosterone (ng/mL)	–0.079	0.171†	0.040	0.490*
Free testosterone (pg/mL)	0.054	0.348†	0.210	<0.001*
DHEA-S (µg/dL)	0.009	0.882†	0.040	0.486*

AMH: Anti-Mullerian hormone; BMI: Body mass index; DHEA-S: Dehydroepiandrosterone sulfate; FSH: Follicular stimulating hormone; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment of insulin resistance; LH: Luteinizing hormone; 17-OHP: 17-hydroxy progesterone; TSH: Thyroid stimulating hormone; T4: Free thyroxine.

*Pearson correlation coefficient, †Spearman correlation coefficient.

AMH is secreted from early antral to small antral follicles in the ovaries and indicates the number of growing follicles. AMH also indirectly reflects the number of residual primordial follicles or ovarian follicular reserve.[16] AMH plays an important integral role in ovarian functions with its local growth factor and cellular differentiation factor effects and its paracrine inhibitory effect on the activation of folliculogenesis.[17] An increase in AMH levels decreases the response of pre-antral and small antral follicles to FSH through decreased FSH-induced aromatase expression and FSH receptor mRNA expression. These alterations cause anovulation by impairing the response of follicles in the ovaries to gonadotropins.[18] As expected, negative correlations between FSH and AMH levels were found in our study population. AMH levels reach the highest level at puberty and decrease with advancing age. Studies have reported that serum AMH is constantly higher in women with PCOS. Abbara et al. reported in 187 non-obese infertile patients that serum AMH levels were higher in women with all three characteristics of PCOS (hyperandrogenism, menstrual irregularities, and polycystic morphology) than in patients without these characteristics.[19] Laven et al. demonstrated elevated serum AMH levels in 106 PCOS women with anovulation than in 41 normo-ovulatory women.[20] In a systemic literature review and meta-analysis, Iliodromiti et al. demonstrated that the sensitivity and specificity for diagnosing PCOS in symptomatic patients were 82.8% and 79.4%, respectively, for a cutoff AMH value of 4.7 ng/mL.[21] Consistently, we found increased AMH levels in our study group, with a mean AMH level of 5.3 ng/mL. Our data confirm the hypothesis that AMH is involved in the pathogenesis of PCOS and may be used as a biomarker for PCOS diagnosis, especially in assessing ovarian reserve. Similar AMH levels in terms of oligomenorrhea were also demonstrated in PCOS patients. Our study indicates that serum AMH levels could not determine the risk of oligomenorrhea in women diagnosed with PCOS. Therefore, serum AMH levels could not be used as a tool to identify menstrual disturbances in PCOS women.

In addition, a relationship between AMH and prolactin in PCOS patients was shown. This could be explained by the potential sharing of a common pathophysiological link. The associations between PCOS and IR, dyslipidemia, and disturbed glucose metabolism have been reported a few decades ago. Excessive androgen in PCOS women can cause induced IR, elevated adipose lipid accumulation

and dyslipidemia, and an unbalanced LH/FSH ratio.[22,23] IR may promote adrenal and ovarian hormone production, increase LH secretion frequencies, and decrease hepatic sex hormone-binding globulin synthesis and, thus, increase testosterone activity.[23,24] Increased gonadotropins may also induce androgen synthesis in ovarian theca cells and reduce estrogen expression and aromatization in granulosa cells, whereas high androgen and decreased estrogen can advance the LH/FSH ratio.[25] These describe PCOS as a vicious cycles. Prolactin and AMH can synergistically contribute to these metabolic processes. Glintborg et al. showed in 1007 patients with PCOS that prolactin levels were associated with metabolic risks and cortisol levels.[23] Yang et al. demonstrated in 2052 PCOS patients that serum prolactin levels were correlated with glucose, lipid profile, hepatic profile, and BMI retrospectively.[26] Recently, in another study, the same researchers showed that prolactin levels were associated with HOMA-IR and fasting insulin levels in 792 PCOS patients.[27] AMH is also involved in the mechanism of metabolic changes in PCOS, such as prolactin. Jun et al. demonstrated that serum AMH levels were related to HOMA-IR, triglycerides, high-density lipoprotein cholesterol, and adiponectin levels in PCOS women. [28] Consistent with the literature, our study indicates that AMH and prolactin are involved separately or jointly in the pathogenesis of PCOS and may be substantial causes of metabolic disturbances in PCOS patients.

The low number of patients and retrospective design were among the limitations of the current study.

CONCLUSION

Our study demonstrated similar AMH and prolactin levels in PCOS women in terms of oligomenorrhea. However, we found a relationship between AMH and prolactin, suggesting that these metabolites are involved in the pathophysiology of PCOS and may be substantial causes of metabolic disturbances in PCOS patients.

Disclosures

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