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Cardiovascular risk factors in polycystic ovary syndrome; the relationship of dyslipidemia and obesity

Şefik Gökçe, Dilşad Herkiloğlu

Yeni Yüzyıl University Private Gaziosmanpaşa Hospital, Obstetrics and Gynecology Department, Gaziosmanpaşa, İstanbul, Turkey

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ABSTRACT

Aim: The abnormal endocrinological picture that occurs in polycystic ovary syndrome (PCOS) has been shown to affect many systems and can lead to a wide variety of complications. In the present study, it was aimed to evaluate the role of obesity and anti-Mullerian hormone (AMH) level in the development of PCOS and to determine potential cardiac risk factors in PCOS.

Material and Method: The present study included 62 patients diagnosed with PCOS and 45 healthy women. Demographic data and laboratory results of all women were collected from hospital automation system records and were analyzed.

Results: The mean body mass index (BMI) (p=0.041), total cholesterol (p=0.038), triglyceride (p=0.022), very low-density lipoprotein (VLDL) cholesterol (p=0.003), and AMH (p<0.001) levels were significantly higher in the patient group than in the control group. The rate of women with BMI value ≥25 kg/m² was significantly higher in the patient group than that of the control group (57.6% vs. 35.6%; p=0.026). In addition, having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development. In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for the diagnosis of PCOS.

Conclusion: In our study, it was concluded that obesity plays a role in the development of PCOS, the level of AMH in PCOS patients increases significantly enough to gain a diagnostic value. In addition, it was concluded that a significant dyslipidemia develops in PCOS, and that this might be a risk for the development of cardiovascular disease in the future.

Keywords: Polycystic ovary syndrome (PCOS), anti-Mullerian hormone, body mass index, dyslipidemia, cholesterol.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a polygenic endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. It is seen in 6-10% of women of reproductive age (1,2). It has been reported that hereditary ovarian steroidogenesis and follicular development play a role in the emergence of PCOS (1).

It has been reported that rapid gonadotropin-releasing hormone (GnRH) stimulation, over-release of luteinizing hormone (LH) and insufficient release of follicle-stimulating hormone (FSH) in PCOS lead to excessive androgen production in ovaries and cause ovulatory dysfunction (1,3). In this clinical picture, it has also been shown that insulin resistance occurs, and this leads to compensatory hyperinsulinemia, resulting in increased excess androgen release from the ovaries and adrenaline. With increased androgen production, conditions such as hirsutism, menstrual abnormalities occur (1,4).

In PCOS, 12 or more cysts with diameters of 2-9 mm are formed in one or both of the ovaries. In addition, the menstrual cycle continues at intervals of less than 21 days or longer than 35 days. In addition to these clinical pictures, hirsutism in PCOS has been reported to cause psychological abnormalities such as depression and anxiety (1,5,6).

It has been shown that the abnormal endocrinological manifestations in PCOS affect many systems and can lead to a wide variety of complications (4,5). It has been reported that women with PCOS have an increased risk for infertility, endometrial hyperplasia, cancer, abnormal glucose metabolism, metabolic syndrome, dyslipidemia, obstructive sleep apnea, depression and anxiety (1). It has been shown that increased anti-Mullerian hormone in PCOS may be associated with dyslipidemia and cardiovascular disorders (1,4).

Corresponding Author: Şefik Gökçe, sefgokce@gmail.com

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In the present study, it was aimed to evaluate the role of obesity and AMH level in the development of PCOS and to determine potential cardiac risk factors in PCOS.

MATERIAL AND METHOD

The study was approved by Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (Date: 21.08.2015, Decision No: 138). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 62 patients diagnosed with PCOS and 45 healthy women who admitted to the Gynecology and Obstetrics clinics of our tertiary hospital. This study was planned retrospectively. Demographic data and laboratory results of all women were collected from hospital automation system records and were analyzed. Informed consent was obtained from all participants. PCOS was diagnosed using Rotterdam criteria (10). According to the Rotterdam criteria, a clinical diagnosis of PCOS requires that a patient present with two of the following symptoms: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. In addition, the presence of hirsutism, one of the hyperandrogenism findings, was evaluated using the Ferriman-Gallwey scoring system (11). Physical and gynecological examinations, pelvic ultrasounds and peripheral venous blood sampling were performed on the 2nd or 3rd day of a participant's menstrual cycles. All women were examined and pelvic ultrasound scans were performed by the same gynecologist using a 7.0 MHz vaginal transducer (Voluson 730, GE Healthcare, USA) (6,7).

Patients who received medications for some diseases such as Cushing syndrome, congenital adrenal hyperplasia, pregnancy, androgen-secreting tumors, oral contraceptives, antilipidemic and/or antihypertensive drugs, steroids, diabetic drugs, anticoagulants or antiplatelet drugs were excluded from the study.

After one night fasting, blood samples of the patients were taken from the antecubital veins. For serum, biochemical and hormonal evaluation; complete blood counts were measured using fluorescent flow cytometry or electrical impedance method. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), antimullient hormone and total testosterone were determined using commercially available enzyme-dependent immunosorbent assay (ELISA) kits (eBioscience). Glucose, insulin, total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol levels were measured with AutoAnalyzer.

Statistical Analysis

All statistical analyzes in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as numbers and percentages. In terms of categorical variables, comparisons between groups were made with Pearson's Chi Square test and Fisher's exact test. Kolmogorov-Smirnov Test was used to confirm whether the continuous variables were suitable for normal distribution. The differences between the groups in terms of continuous variables were analyzed using Student's t Test, and the comparison of mean values between multiple groups by variance analysis. The capacity of the AMH serum level to predict PCOS presence was analyzed using receiver operating characteristic (ROC) curve analysis. Risk coefficient of categorical variables was evaluated by logistic regression analysis and given as "odds ratio". The results were evaluated within the 95% confidence interval, and $p<0.05$ values were considered significant. Bonferroni correction was made where appropriate.

RESULTS

The mean age was 27.0±3.2 years in the patient group, and was 27.9±4.0 years in the control group. The mean body mass index (BMI) ($p=0.041$), total cholesterol ($p=0.038$), triglyceride ($p=0.022$), and very low-density lipoprotein (VLDL) cholesterol ($p=0.003$) levels were significantly higher in the patient group than that in the control group. AMH (12.0 vs. 3.0 ng/mL; $p<0.001$), total testosterone ($p<0.001$) and free testosterone ($p<0.001$) levels were significantly higher in the patient group than that the control group, and FSH was significantly lower ($p<0.001$). There was no significant difference between groups in terms of hemoglobin A1c (HbA1c) and insulin levels ($p>0.05$ for both) (**Table 1**).

Having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development. The rate of women with BMI value ≥25 kg/m² was significantly higher in the patient group than that of the control group (57.6% vs. 35.6%; $p=0.026$). In addition, having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development.

BMI groups were similar in terms of the mean cholesterol, triglyceride, glucose and HbA1c levels ($p>0.05$ for each) (**Table 2**).

In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for diagnosis of PCOS (AUC: 0.883; $p<0.001$; LB: 0.819; UB: 0.947; CI 95%) (**Figure 1**) .

Table 1. Comparison between polycystic ovarian syndrome patients and the control group in terms of the mean age, body mass index, cholesterol and hormone levels.

	PCOS (n=62)		Control (n=45)		p
	Mean	SD	Mean	SD	
Age (Years)	27.0	3.2	27.9	4.0	0.236
BMI (Kg/m²)	26.7	4.8	24.7	4.8	0.041
Ferriman Gallwey score	15.4	8.7	2.3	1.6	<0.001
Total Cholesterol (mg/dL)	180.4	35.8	167.5	23.6	0.038
Triglycerides (mg/dL)	112.8	70.5	86.4	33.7	0.022
LDL Cholesterol (mg/dL)	115.3	31.5	109.6	27.9	0.332
HDL Cholesterol (mg/dL)	46.5	10.7	49.3	9.2	0.159
VLDL Cholesterol (mg/dL)	22.3	13.6	15.8	4.9	0.003
Apolipoprotein A Subgroups (mg/dL)	153.5	23.4	155.4	15.0	0.636
Glucose (mg/dL)	90.9	11.7	92.5	7.9	0.425
Hba1c (mmol/L)	5.4	0.4	5.5	0.3	0.468
Insulin (mIU/L)	11.9	7.6	9.6	6.1	0.089
Anti-Müllerian Hormon (ng/mL))	12.0	8.0	3.0	2.8	<0.001
1,4-Delta Androstenedion (ng/mL)	3.9	1.3	2.4	1.0	<0.001
Dehydrotestosterone (ng/dL)	346.6	113.6	385.2	375.5	0.447
Total Testosterone (ng/dL)	0.5	0.2	0.3	0.1	<0.001
Free Testosteron (ng/dL)	2.6	1.0	1.8	0.9	<0.001
Progesterone (ng/dL)	1.1	2.3	1.9	3.8	0.164
17-OH Progesterone (ng/dL)	1.9	1.8	1.2	0.9	0.016
Dehydroepiandrosterone Sulfate (µg/dL)	287.3	110.9	256.4	114.4	0.164
FSH (IU/mL)	4.6	1.2	6.0	2.0	<0.001
LH (IU/L)	6.0	2.8	6.7	4.7	0.679
Prolactin (ng/dL)	16.3	12.7	18.6	14.5	0.398
Estradiol (pg/dL)	70.8	58.7	58.2	36.0	0.205
TSH (mIU/L)	1.7	0.8	1.9	1.1	0.169
T3 (ng/dL)	2.9	0.4	10.5	50.5	0.243
T4 (ng/dL)	1.0	0.1	1.0	0.2	0.882

PCOS: Polycystic ovary syndrome, SS: Standard deviation, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone. T3: Triiodothyronine T4: Thyroxine

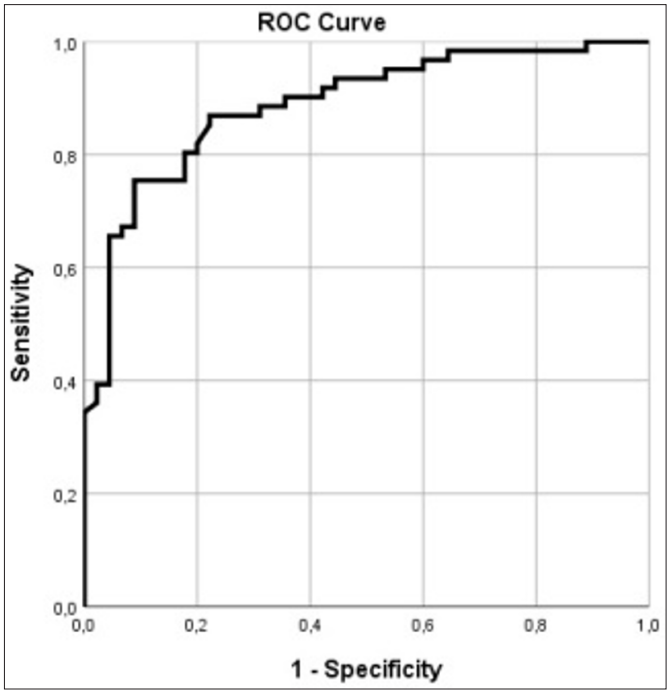

Figure 1. In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for the diagnosis of PCOS (AUC: 0.883; p<0.001; LB: 0.819; UB: 0.947; CI 95%).

Table 2. Mean values according to body mass index (BMI) in patient group and BMI distribution according to patient and control groups.

	BMI ≥25 (kg/m²) (n=50)		BMI<25 (kg/m²) (n=57)		p
	Mean	SD	Mean	SD	
Cholesterol (mg/dL)	181.2	37.7	180.4	35.7	0.931
Triglyceride (mg/dL)	127.7	79.4	98.4	55.3	0.119
Glucose (mg/dL)	91.1	14.4	91.0	7.7	0.973
HbA1c (mmol/L)	5.4	0.2	5.4	0.6	0.791
	n	%	n	%	
PCOS	34	57.6	25	42.4	0.022
Control	16	35.6	29	64.4	

BMI: Body mass index, SS: Standard deviation, PCOS: Polycystic ovary syndrome. HbA1c:glycosylated hemoglobin

DISCUSSION

Polycystic ovarian syndrome is an endocrinological disease that occurs in women of reproductive age due to many factors. The resulting endocrine abnormalities affect many systems in women and cause various complications. Disorders in women with PCOS significantly impair their quality of life (1,9,10). In our study, clinical features of women with PCOS were examined, and especially obesity and dyslipidemia rates were found significantly higher.

It has been stated that anti-Mullerian hormone is released from granulosa cells in small antral and pre-antral follicles and plays a role in early follicular development (11,12). It has been suggested that AMH can be used as a hormonal marker to determine the number of follicles in the ovary (13,14). Accordingly, it has been stated that AMH serum levels can reflect ovarian reserve indirectly and remain stable from cycle to cycle (11,14). It has been reported that the level of AMH in PCOS patients is significantly higher than that of healthy individuals, and this condition may be related to androgen (11,12,15). Karakas et al. (16) reported in their meta-analysis that AMH was a marker that can be used in the diagnosis, in predicting the prognosis and in predicting the response to infetrility therapy in the PCOS cases.

The total number of ovarian follicles increases in PCOS. This is especially true for antral follicles that produce large amounts of AMH (17,18). Several studies have shown that serum AMH levels above 5 ng/ml (35.7 pmol/L) can be used for the diagnosis of PCOS (19,20). Questions have been raised as the use of AMH in adolescent patients that they may have PCO morphology without the syndrome (21). However, the mean AMH concentration in adolescent girls has been shown to be about 3 ng/ml, regardless of ethnic origin (22). Therefore, serum AMH is still a valuable tool for diagnosing PCOS during adolescence. An advantage of AMH measurement is that it can be performed when transvaginal ultrasound is not available. It provides quantitation of cysts, and higher AMH concentrations may indicate more severe disease (23). The highest levels of AMH are seen when all three components of PCOS (hyperandrogenemia, anovulation and PCO) are present. Hyperandrogenism has the weakest association with AMH (19). Obesity may cause a relative decrease in AMH in PCOS patients (24). During ovulatory menstrual cycles, AMH levels are approximately 8% lower during the luteal phase compared to the follicular phase (25). However, this is not an important factor for the diagnosis of PCOS because most patients have anovulation. Combined contraceptives suppress AMH levels by about 30% to 50% over time, regardless of the route of administration (26,27). GnRH agonist leuprid administration also suppresses AMH (28). Wissing et al. (29) reported that AMH, along with BMI and androgen level, could be a reliable marker for PCOS diagnosis. All three ELISAs detecting different parts of the AMH molecule detected significantly higher levels in women with PCOS compared to control women. The relative distribution of AMH isoforms did not differ between women with PCOS and control women. AMH isoforms alone and in combination with key features predicted PCOS with close to 100% area under the receiver operating characteristic curve. It is noticeable that based on circulatory androgens, BMI, and AMH measurements, the ROC area reached 97% without measurement of AFC (15). Fleming et al. (30) found that serum AMH levels were significantly higher in PCOS patients with insulin resistance in their study conducted using HOMA-R for detection of insulin. De Kat et al. (31) found a significant relationship between age-specific AMH levels and total cholesterol levels. They also reported that high AMH levels significantly increased the risk of cardiovascular disease, which was independent of cholesterol level (31). In our study, there was no significant relationship between AMH levels and cholesterol and triglyceride levels in PCOS patients. These findings show that AMH levels have various endocrine effects, but it is not clear yet whether there is a relationship between insulin and cholesterol levels.

It has been reported that PCOS is associated with obesity (32). Lim et al. (33) determined a significant relationship between high BMI and PCOS development in their meta-analysis, and they found that high BMI values caused a 3.35-fold higher risk for PCOS development than normal BMI values. In our study, mean BMI was significantly higher in the PCOS group compared to the controls. In the risk analysis, it was determined that having BMI value of over 25 kg/m² causes 2.47-fold higher risk for PCOS development. These findings show that PCOS patients are more obese than healthy women, and obesity significantly increases the risk of PCOS development.

Neuroendocrine abnormalities may play an important role in the pathophysiology of PCOS, that they increase LH levels and decrease FSH levels by increasing GnRH (32). Wissing et al (29). found that the mean FSH level was significantly lower and the LH level was significantly higher in the PCOS group. In our study, no significant difference was found between the groups in terms of the mean LH levels. However, the mean FSH level was significantly lower in the PCOS group than the controls. These findings confirm a marked decrease in FSH levels in PCOS patients.

It has been reported that PCOS increases the risk of cardiovascular disease, and the risk increases further with age and with obesity progress (7). PCOS has been reported to be similarly associated with dyslipidemia (32). In addition, obesity has been shown to be associated with dyslipidemia in PCOS patients (33,34). It has been determined that 70% of women with PCOS can develop dyslipidemia (8). However, there is not sufficient evidence about the relationship between cardiovascular disease and PCOS in the long term yet (7). It was reported that the most frequent dyslipidemia picture that PCOS affects is triglyceridemia (8). Wissing et al. (29) found no significant difference between PCOS and control groups in terms of total cholesterol, LDL cholesterol and triglyceride levels. In our study, mean total cholesterol, triglyceride and VLDL cholesterol levels

were significantly higher in the PCOS group compared to the controls. These findings indicate that dyslipidemia develops in PCOS patients, which may cause an increased risk for cardiovascular diseases in the future.

The metabolic difficulties that occur in PCOS are related to insulin resistance and diabetes (7,32). In particular, the relationship between PCOS and obesity has been reported to pose an increased risk for insulin resistance and diabetes (7,8). In the present study, no significant difference was found between the groups in terms of HbA1c, glucose and insulin levels. This might be due to low number of the patients in our study. The present study had some limitations such as retrospective design and small sample size.

CONCLUSION

In the present study, it was concluded that obesity plays a role in the development of PCOS, that the level of AMH in PCOS patients increases significantly enough to gain a diagnostic value, that a significant dyslipidemia develops in PCOS, and that this might be a risk for the development of cardiovascular disease in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (Date: 21.08.2015, Decision No: 138).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. McCartney CR, Marshall JC. Clinical Practice. Polycystic Ovary Syndrome N Engl J Med 2016; 375: 54-4.
2. Meier RK. Polycystic Ovary Syndrome. Nurs Clin North Am 2018; 53: 407-20.
3. Nandi A, Chen Z, Patel R, Poretsky L. Polycystic ovary syndrome Endocrinol Metab Clin North Am 2014; 43: 123-47.
4. Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Pract Res Clin Obstet Gynaecol 2018; 48: 103-14.
5. Li L, Feng Q, Ye M, He Y, Yao A, Shi K. Metabolic effect of obesity on polycystic ovary syndrome in adolescents: a meta-analysis. J Obstet Gynaecol 2017; 37: 1036-47.
6. Bani Mohammad M, Majdi Seghinsara A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev 2017; 18: 17-21.
7. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91: 941-5.
8. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2011; 95: 1073-9.
9. Barthelmess EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. Front Biosci (Elite Ed) 2014; 6: 104-19.
10. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011; 7: 219-231.
11. Łebkowska A, Kowalska I. Anti-Müllerian hormone and polycystic ovary syndrome. Endokrynol Pol 2017; 68: 74-8.
12. Bani Mohammad M, Majdi Seghinsara A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev 2017; 18: 17-21.
13. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91: 941-5.
14. Feldman RA, O'Neill K, Butts SF, Dokras A. Antimüllerian hormone levels and cardiometabolic risk in young women with polycystic ovary syndrome. Fertil Steril 2017; 107: 276-81.
15. Tata B, Mimouni NEH, Barbotin AL, et al. Elevated prenatal anti-Müllerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood. Nat Med 2018; 24: 834-6.
16. Karakas SE. New biomarkers for diagnosis and management of polycystic ovary syndrome. Clin Chim Acta 2017; 471: 248-53.
17. Bhide P, Dilgil M, Gudi A, Shah A, Akwaa C, Homburg R. Each small antral follicle in ovaries of women with polycystic ovary syndrome produces more antiMullerian hormone than its counterpart in a normal ovary: an observational cross-sectional study. Fertil Steril 2015; 103: 537–41.
18. Homburg R, Ray A, Bhide P, et al. The relationship of serum anti-Mullerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study. Hum Reprod 2013: 28: 1077–83.
19. Sahmay S, Atakul N, Aydogan B, Aydin Y, Imamoglu M, Seyisoglu H. Elevated serum levels of anti-Mullerian hormone can be introduced as a new diagnostic marker for polycystic ovary syndrome. Acta Obstet Gynecol Scand 2013; 92: 1369–74.
20. Saikumar P, Selvi VK, Prabhu K, Venkatesh P, Krishna P. Anti Mullerian hormone: a potential marker for recruited non growing follicle of ovarian pool in women with polycystic ovarian syndrome. J Clin Diagn Res 2013; 7: 1866–9.
21. Agapova SE, Cameo T, Sopher AB, Oberfield SE. Diagnosis and challenges of polycystic ovary syndrome in adolescence. Semin Reprod Med 2014; 32: 194–201.
22. Elchuri SV, Patterson BC, Brown MR, Buchanan I, Mertens AC, Meacham LR. Anti-Mullerian hormone levels in American girls by age and race/ethnicity. J Pediatr Endocrinol Metab 2015; 28; 189–93.
23. Koninger A, Koch L, Edimiris P, et al. Anti-Mullerian hormone: an indicator for the severity of polycystic ovarian syndrome. Arch Gynecol Obstet 2014; 290: 1023–30.
24. Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 2009; 296: 238–43.

25. Schiffner J, Roos J, Broomhead D, et al. Relationship between anti-Müllerian hormone and antral follicle count across the menstrual cycle using the Beckman Coulter Access assay in comparison with Gen II manual assay. Clin Chem Lab Med 2017; 55: 1025-33.
26. Bentzen JG, Forman JL. Pinborg A, et al. Ovarian reserve parameters: a comparison between users and non-users of hormonal contraception. Reprod BioMed Online 2012; 25: 612–9.
27. Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. AntiMullerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril 2013; 99: 1305–10.
28. Su HI, Maas K, Sluss PM, Chang RJ, Hall JE, Joffe H. The impact of depot GnRH agonist on AMH levels in healthy reproductive-aged women. J Clin Endocrinol Metab 2013; 98: 1961–6.
29. Wissing ML, Mikkelsen AL, Kumar A, et al. Associations of different molecular forms of antimüllerian hormone and biomarkers of polycystic ovary syndrome and normal women. Fertil Steril 2019; 112: 149-55.
30. Fleming R, Harborne L, MacLaughlin DT, et al. Metformin reduces serum mullerian-inhibiting substance levels in women with polycystic ovary syndrome after protracted treatment. Fertil Steril 2005; 83: 130-6.
31. De Kat AC, Verschuren WM, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Anti-Müllerian hormone trajectories are associated with cardiovascular disease in women: results from the Doetinchem Cohort Study. Circulation 2017; 135: 556-65.
32. Bozdag G, Yildiz BO. Interventions for the metabolic dysfunction in polycystic ovary syndrome. Steroids 2013; 78: 777-81.
33. Glueck CJ, Goldenberg N. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism 2019; 92: 108-20.
34. Caldwell AS, Middleton LJ, Jimenez M, et al. Characterization of reproductive, metabolic, and endocrine features of polycystic ovary syndrome in female hyperandrogenic mouse models. Endocrinology 2014; 155: 3146-59.