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ORIGINAL ARTICLE

C-Reactive Protein, Fibrinogen, Leptin, and Adiponectin Levels in Women with Polycystic Ovary Syndrome

Cagdas Ozgokce[1] · Erkan Elci[2] · Recep Yildizhan[3]

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Abstract

Background and Aim We aimed to compare the levels of clinical, biochemical, hormonal, and metabolic parameters as well as serum CRP, fibrinogen, leptin, and adiponectin in cases with PCOS and control group to investigate whether they play a role in the etiology of the syndrome.

Materials and Methods The present study included a total of 90 subjects, 45 subjects were diagnosed with PCOS ($n=45$) and 45 subjects served as control group ($n=45$). Serum CRP, fibrinogen, leptin, and adiponectin levels were analyzed for each subject.

Results Serum CRP, fibrinogen, and leptin were found to be higher (statistically significant) in the group with PCOS as compared to the control group ($p<0.05$). Serum Adiponectin was higher in the control group (statistically significantly) as compared with the patients in the PCOS group ($p<0.05$).

Conclusion CRP and fibrinogen (cardiac risk factor markers) increase in women with PCOS. The levels of leptin which affects metabolism increase, whereas the levels of adiponectin decrease.

Keywords PCOS · CRP · Leptin · Adiponectin · Fibrinogen

Introduction

PCOS is one of the most frequently seen endocrinopathies and encountered in 5–10% of women in the reproductive age [1]. Infertility due to anovulatory disorders, persistent acne, oligo-amenorrhea, and hirsutism were reported in 75%, 80%, 90%, and 90% of the cases with PCOS, respectively [2, 3]. Although the etiopathogenesis of PCOS is not completely clear yet, genetic predisposition, impaired gonadotropin secretion, impaired ovarian steroid hormone synthesis, hyperinsulinemia, and insulin resistance (IR) play a role in its pathogenesis [5].

C-reactive protein (CRP) is an acute-phase reactant that is responsible for the immune system response. CRP is associated with IR and endothelial dysfunction in the women with PCOS [4] and high levels of CRP may be responsible for long-term cardiovascular complications in the women with PCOS [4, 5].

Increased fibrinogen levels were reported to be associated with an increased risk for cardiovascular disease [6]. Some studies have considered fibrinogen as a marker for the early diagnosis of PCOS [10], whereas some studies have reported that the importance of increased fibrinogen levels as a marker in the patients with PCOS is controversial [7].

Adiponectin is an adipocytokine secreted by adipose tissue with important metabolic effects [8]. Adiponectin has anti-inflammatory, anti-atherogenic, cardioprotective, and insulin-sensitizing characteristics [8]. Although it is secreted by adipose tissue, its circulating levels decrease in

Cagdas Ozgokce is a Gynecologist and Obstetrician, Department of Obstetrics and Gynecology, Private Van Akdamar Hospital, Van, Turkey. Erkan Elci is a Gynecologist and Obstetrician, Department of Obstetrics and Gynecology, University of Healty Sciences Umraniye Training and Research Hospital. Recep Yildizhan is a Professor, Department of Perinatology, Demiroglu Bilim University Faculty of Medicine.

✉ Erkan Elci
dr.erkanelci@gmail.com

1 Department of Obstetrics and Gynecology, Private Van Akdamar Hospital, Van, Turkey

2 Department of Obstetrics and Gynecology, University of Healty Sciences Umraniye Training and Research Hospital, Istanbul, Turkey

3 Department of Perinatology, Demiroglu Bilim University Faculty of Medicine, Abide-I Hürriyet Street, No: 164, Şişli, Istanbul, Turkey

the clinical picture of obesity whereas weight loss increases its levels [9]. Adiponectin is an adipocytokine with insulin-sensitizing and antiatherosclerotic characteristics identified in recent times [10].

Leptin synthesis in subcutaneous adipose tissue is higher when compared with visceral adipose tissue [11]. Leptin levels in women with PCOS are still controversial, some studies have demonstrated elevated leptin levels whereas other studies have encountered no difference in leptin levels [11, 12].

The present study aimed to compare the levels of clinical, biochemical, hormonal and metabolic parameters and laboratory values of serum CRP, fibrinogen, leptin, and adiponectin in cases with PCOS and in control group to investigate whether they play a role in the etiology of the syndrome.

Materials and Methods

The present study was conducted in the Obstetrics and Gynecology Clinic of YYU Research and Practice Hospital between February 2009 and July 2009 after being approved by The Ethics Committee of YYU Medical Faculty. The women included in the study were instructed about the study and their verbal and written consent was obtained.

The study group included 45 non-obese women (BMI < 30 kg/m^2) aged between 18 and 30 years who were admitted to our clinic with complaints of menstrual irregularity (oligo-amenorrhea), clinical findings of hyperandrogenism (hirsutism, acne, oily skin, androgenic alopecia) and polycystic ovaries (12 or more cysts in each ovary, presence of follicles with a diameter of 2–9 mm and/or ovarian volume above 10 cm^3) on ultrasonographic examination. Patients were diagnosed with PCOS according to the criteria of Androgen Excess Society (AES) using biochemical and hormonal tests. The control group included 45 non-obese healthy women (BMI < 30 kg/m^2) at similar ages and without PCOS according to ultrasonographic, biochemical, and hormonal tests and without complaints of menstrual irregularity and findings of hyperandrogenism.

Data of the patients in the study and control groups were recorded in the previously prepared research forms. Data on age, WHR, BMI, menstrual regularity, systolic-diastolic blood pressure, dysmenorrhea, hirsutism, acne, alopecia androgenetica, acanthosis nigricans, Ferriman-Gallwey score (FGS), hemogram, biochemistry, CRP, fibrinogen, albumin, globulin, lipid profile (HDL, LDL, VLDL, TG), hormonal parameters (LH, FSH, E2, PRL, tT, SHBG, DHEAS, Androstenedione), insulin, IGFBP-1, and Somatomedin-C levels were requested and recorded in the research forms mentioned above. Insulin resistance (IR) was assessed using the Homeostasis Model Assessment Method-Insulin Resistance (HOMA-IR). HOMA-IR index was calculated according to the formula = [fasting plasma glucose (mmol/l) X fasting plasma insulin concentration (mU/ml)]/22.5 and insulin resistance was defined as the HOMA-IR value > 2.5 [19]. Free androgen index (FAI) was calculated according to the Formula = Total Testosterone (nmol/l)/SHBG (nmol/l) $\times 100$.

Blood samples were taken after overnight fasting on the third day of the menstrual period and centrifuged at 1500 rpm for 15 min (Nu¨ve NF 800R, Ankara, Turkey). Serum samples were then collected into microcentrifuge tubes and stored at -80 °C until the day on which the last blood sample was drawn. Levels of FSH, LH, E2, tT, DHEAS, and insulin were determined by the chemiluminescence immunoassay using an Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA).

Measurement of Serum CRP, Fibrinogen, Leptin, and Adiponectin

Fibrinogen measurement: Quantitative determination of fibrinogen plasma levels was done by the clotting method of Clauss with TC Fibrinogen Reagent® (Cryopep, Montpellier, France).

CRP measurement: AssayMax Human ELISA kit (Assaypro Co. Ltd., St. Charles, MO, USA) was used. The range of the test was 0.25–16 ng/ml.

Adiponektin measurement: AssayMax Human Adiponektin (Acrp30) ELISA kit (Assaypro Co. Ltd., St. Charles, MO, USA) was used. The range of the test was 0–25 pg/ml.

Leptin measurement: AssayMax Human ELISA kit (Assaypro Co. Ltd., St. Charles, MO, USA) was used. The range of the test was 0–20 ng/ml.

All measurements were performed at 450-nm optical wave density.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS, Version 22, IBM Corp., Armonk, NY) program was used for all statistical analyses. Descriptive statistics such as median and standard deviation values were for continuous variables. Uncertainty was expressed as 95% Confidence İntervals (CI). Student's t test was used to determine differences in the means. The Pearson correlation test was used to find the relation between the variables. Chi-square analysis was performed to assess the differences in the proportions between the subgroups. A value of $p < 0.05$ was considered statistically significant.

Results

No statistically significant differences were found between the groups in terms of age. The patients with PCOS had statistically significant higher values of hemoglobin,

systolic-diastolic blood pressure, acne, acanthosis nigricans, menstrual irregularity and a statistically significant lower value of dysmenorrhea. No statistically significant difference was detected between the groups regarding alopecia androgenetica. Waist/hip ratio (WHR), BMI, and FGS values were found to be higher in the patients with PCOS as compared to the control group. The demographic and basic clinical features of the study population are shown in Table 1.

On analysis of lipid profile in the polycystic ovary syndrome group, statistically significant higher values of LDL, triglycerides, total cholesterol, and VLDL were found in the group with PCOS whereas they had lower levels of HDL. It was encountered that PRL was high (statistically significant) and was directly proportional with high levels of E2 although FSH was lower than LH in the women with PCOS. With respect to the components associated with androgen and insulin sensitivity, insulin, Somatomedin C, HOMA-IR, total testosterone, FAI, and DHEAS levels were found to be higher (statistically significant) in the group with PCOS. IGFBP-1 and SHBG were detected to be lower (statistically significant) in the group with PCOS. Androstenedione levels were higher in the group with PCOS than the control group; however, the difference between the groups was not statistically significant. CRP, fibrinogen, and leptin levels were found to be higher (statistically significant) in the group with PCOS than the control group, whereas adiponectin was detected to be lower (statistically significant) in the group with PCOS than the control group. The results of the biochemical and hormone analyses are shown in Table 2.

The correlation between the clinical, biochemical, and hormonal analyses of the serum HOMA-IR, insulin, fibrinogen, adiponectin, and leptin levels in the women with PCOS is shown in Table 3. CRP was found to have a positive correlation with HOMA-IR, fibrinogen, and leptin, while its strongest correlation was with fibrinogen. Fibrinogen positively correlated with waist/hip ratio, LH, HOMA-IR, insulin, and CRP. Fibrinogen demonstrated the closest correlation between insulin and CRP values. Adiponectin showed a positive correlation with HDL and SHBG whereas it negatively correlated with LDL, tT, FAI, HOMA-IR, CRP, Fibrinogen, and leptin. Leptin was found to have a positive correlation with HOMA-IR, insulin, CRP, and fibronogen and a negative correlation with adiponectin. Leptin was found to have a positive correlation with HOMA-IR, insulin, and CRP while its strongest correlation was with HOMA-IR and a negative correlation with adiponectin.

Discussion

PCOS is one of the most frequently seen endocrinopathies and encountered in 5-10% of women in the reproductive age group [1]. PCOS carries long-term health risks like Type 2 DM, dyslipidemia, cardiovascular disease, infertility, endometrial and breast cancer as a multisystemic syndrome [4]. The patients with PCOS manifest clinical findings such as hirsutism, acne, and seborrhea as reflections of hyperandrogenism as well as menstrual irregularities due

Table 1 Demographic and basic clinical features of the study groups

	Control ($N=45$)	PCOS ($N=45$)	Value (p)
Age (years)	21.67 ± 2.992	22.96 ± 4.280	0.101
Hemoglobin (gr/dL)	12.68 ± 0.631	13.26 ± 1.269	0.007*
Systolic-blood pressure (SBP)(mmhg)	109.56 ± 12.424	124.44 ± 11.192	0.001*
Diastolic blood pressure (DBP)(mmhg)	69.56 ± 10.651	78.78 ± 7.845	0.001*
Acne			
Positive	2(4.4%)	36(80%)	<0.001*
Negative	43(95.6%)	9(20%)	<0.001*
Acanthosis nigricans (AN)			
Positive	1(2.2%)	12(26.7%)	0.001*
Negative	44(97.8%)	33(73.3%)	0.001*
Alopecia androgenetica (AA)			
Positive	0(0%)	3(6.7%)	0.078
Negative	45(100%)	42(93.3%)	0.078
Dysmenorrhea			
Positive	39(86.7%)	14(31.1%)	<0.001*
Negative	31(13.3%)	31(68.9%)	<0.001*
Menstruele cyclus			
Regular	45(100%)	3(6.7%)	<0.001*
Irregular	0(0%)	42(93.3%)	<0.001*

* Statistical significance was defined as $p < 0.05$

Table 2 Clinical and biochemical parameters of healthy women and PCOS

	Control	PCOS	Value (*p*)
Anthropometric measurements			
Waist-to-hip ratio (cm)	0.876 ± 0.165	0.945 ± 0.223	0.001*
BMI(kg/m2)	22.644 ± 2.079	25.733 ± 2.136	0.001*
FGS	5.20 ± 1.036	12.09 ± 2.032	0.001*
Lipid profiles			
HDL (mmol/L)	59.36 ± 17.090	54.22 ± 3.450	0.05*
LDL (mmol/L)	70.11 ± 6.076	98.52 ± 32.689	0.001*
TG (mmol/L)	114.64 ± 3.465	138.47 ± 63.782	0.014*
TC (mmol/L)	142.60 ± 14.104	178.24 ± 37.979	0.001*
VLDL (mmol/L)	22.55 ± 8.517	35.36 ± 5.428	0.001*
Hormonal components			
PRL(mg/dl)	14.40 ± 10.254	19.92 ± 2.174	0.001*
LH (mU/ml)	4.43 ± 1.169	8.34 ± 4.077	0.001*
FSH (mU/ml)	8.11 ± 1.068	5.37 ± 2.006	0.001*
E2 (pg/ml)	42.13 ± 10.039	79.19 ± 79.494	0.003*
Insulin sensitivity and glucose tolerance			
İnsülin (U/ml)	5.05 ± 0.686	14.36 ± 10.652	0.001*
HOMA-IR	1.5 ± 0.87	3.5 ± 2.2	0.001*
IGFBP-1	5.73 ± 0.527	4.69 ± 2.086	0.002*
Somatomedin C (ng/ml)	47.81 ± 39.282	172.31 ± 76.063	0.001*
Androgens			
Total testesteron (ng/l)	2.3 ± 0.65	7.2 ± 5.94	0.001*
SHBG (nmol/l)	135.53 ± 18.531	45.72 ± 21.672	0.001*
FAI (Free Androgen Index)	1.69 ± 2.278	15.74 ± 6.56	0.001*
DHEAS (ug/dl)	70.80 ± 7.933	237.33 ± 134.272	0.001*
Androstenedion (ng/dl)	3.39 ± 1.480	4.52 ± 3.622	0.063
CRP (ng/ml)	3.26 ± 0.699	5.37 ± 6.377	0.030*
Fibrinojen (mg/dl)	151.33 ± 16.586	279.48 ± 57.616	0.001*
Adiponektin (pg/ml)	6.40 ± 2.447	5.10 ± 1.915	0.046*
Leptin (ng/ml)	7.55 ± 2.017	9.10 ± 2.520	0.001*

Values are expressed as mean ± SD. *BMI* Body Mass Index, *FGS* Ferriman–Gallwey score, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *TG* triglyceride, *TC* Total Cholesterol, *PRL* prolactine, *LH* luteinizing Hormone, *FSH* thyroid-stimulating hormone, *E2* estradiol B, *HOMA-IR* Homeostasis Model Assessment Method-Insulin Resistance, *SHGB* sex hormone-binding globulin, *DHEAS* Dehydroepiandrosterone, *FAI* Free Androgen Index, *CRP* C-reactive protein

* Statistical significance was defined as $p < 0.05$

to oligo-anovulation [13]. Clinically, there are one or more combinations of increased plasma androgen levels as well as clinical findings of hyperandrogenemia such as hirsutism, seborrhea, and acne [13].

The studies conducted on CRP and fibrinogen as the cardiovascular risk markers reported different outcomes. Bickerton et al. found no statistically significant difference between the women with and without PCOS in terms of these parameters [14]. On the other hand, Nasiek et al. evaluated CRP and fibrinogen levels in obese and non-obese women with PCOS in their study and reported that CRP levels were high in both groups whereas no difference was found between the groups regarding fibrinogen levels [15]. Elci et al. found that CRP and fibrinogen levels were high in the obese and non-obese patients with PCOS [4]. In our study fibrinogen levels increased in parallel to CRP levels and that these parameters positively correlated with insulin and insulin resistance and negatively correlated with adiponectin. It was encountered that CRP and fibrinogen (cardiovascular risk markers) increased whereas antiatherosclerotic and anticardiogenic adiponectin decreased.

Adiponectin is a adipocytokine that has important metabolic effects and is secreted by adipose tissue [16]. It has been reported that adiponectin may be considered as antidiabetic, anti-inflammatory, and antiatherosclerotic [17]. It was determined that plasma adiponectin concentration negatively correlated with adipocytes, WHR, diabetic dyslipidemia, cardiovascular disease, and IR [18]. However,

Table 3 Correlation between HOMA-IR, insulin, CRP, fibrinogen, adiponectin, leptin and clinical, hormonal, metabolic parameters in women with PCOS

	HOMA-IR	Insulin (U/ml)	CRP (ng/ml)	Fibrinogen (mg/dl)	Adiponectin (pg/ml)	Leptin (ng/ml)
Age (years)	0.130	−0.157	0.102	0.098	−0.126	0.189
Waist–hip ratio (cm)	0.410*	0.398*	0.101	0.398*	−0.203	0.307
BMI (kg/m2)	0.453*	0.356	0.230	0.124	−0.267	0.310
SBP (mmHg)	0.165	0.213	0.225	0.292	0.082	0.196
DBP (mmHg)	0.278	0.147	0.017	0.154	0.121	0.019
Ferriman-galway Skoru (FGS)	0.360	0.345	0.362	0.383	−0.053	0.164
HDL (mg/dl)	−0.296	−0.204	−0.193	−0.344	0.395*	−0.247
LDL (mg/dl)	0.289	0.138	0.126	0.224	−0.413*	0.263
Trigliserid (mg/dl)	0.221	0.420*	0.304	0.171	−0.238	0.273
VLDL (mg/dl)	0.245	0.311	0.179	0.138	−0.166	0.269
Total cholesterol (mg/dl)	0.389*	0.345	0.108	0.123	−0.289	0.242
Albumin (g/dl)	−0.119	−0.213	0.295	−0.029	0.255	0.079
Globülin (g/dl)	0.278	0.219	0.112	0.254	0.034	0.106
SHBG (nmol/l)	−0.276	−0.343	−0.169	−0.224	0.355*	−0.245
LH (mU/ml)	0.371	0.278	0.104	0.404*	−0.308	0.301
FSH (mU/ml)	0.167	0.197	0.081	0.015	0.278	0.147
E2 (pg/ml)	0.185	0.224	0.259	0.209	0.306	0.147
Total testesteron (ng/ml)	0.469*	0.367	0.351	0.114	−0.389*	0.294
FAI	0.475*	0.398*	0.237	0.275	−0.467*	0.248
DHEAS (ug/dl)	0.367	0.197	0.367	0.263	−0.186	0.303
HOMA-IR	1	0.787**	0.469*	0.386*	−0.346*	0.643**
Insulin (U/ml)	0.787**	1	0.126	0.615**	−0.329	0.458*
CRP (ng/ml)	0.469*	0.126	1	0.527**	−0.362*	0.406*
Fibrinogen (mg/dl)	0.386*	0.615**	0.527**	1	−0.443*	0.327
Adiponectin (pg/ml)	−0.346*	−0.3629	−0.362*	−0.443*	1	−0.325*
Leptin (ng/ml)	0.643**	0.458*	0.406*	0.327	−0.325*	1

BMI Body Mass Index, *FGS* Ferriman–Gallwey score, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *TG* triglyceride, *TC* Total Cholesterol, *PRL* prolactine, *LH* luteinizing Hormone, *FSH* thyroid-stimulating hormone, *E2* estradiol B, *HOMA-IR* Homeostasis Model Assessment Method-Insulin Resistance, *SHGB* sex hormone-binding globulin, *DHEAS* Dehydroepiandrosterone, *FAI* Free Androgen Index, *CRP* C-reactive protein

* Statistical significance was defined as $p < 0.05$

** Statistical significance was defined as $p < 0.01$

the relationship of adiponectin levels with hyperinsulinemia, adipose tissue, or hyperandrogenism is controversial in many studies. In addition, it has been reported that plasma adiponectin concentration negatively correlated with hyperinsulinemia and IR rather than obesity [18, 19]. Some studies have shown that adiponectin level is low in subjects with a high BMI without considering the presence of PCOS [10, 20, 21]. Adiponectin correlated with IR, whereas it showed no correlation with hyperandrogenism in women with PCOS [22]. We have observed in our study that adiponectin level decreased as the BMI increased and that the adiponectin level is statistically lower than the control group in the patients with PCOS. However, adiponectin was not found to correlate statistically with BMI and WHR. Adiponectin negatively correlated with HOMA-IR and insulin while it showed the strongest negative correlation with FAI.

Leptin levels positively correlated with insulin levels [23]. Insulin increases the synthesis and secretion of leptin [23]. It is considered that insulin increases the secretion of leptin since insulin was found to increase the synthesis of leptin mRNA [24]. A study conducted on the relationship between leptin and BMI has reported that BMI correlated with leptin; however, the authors have found no relationship between leptin and insulin [25, 26]. Another study has detected that there was no statistically significant difference between the PCOS and control groups in terms of serum leptin levels [27]. A meta-analysis has reported that the patients with PCOS had high leptin levels and that high leptin levels correlated with IR, metabolic disorder, infertility, and even cardiovascular diseases in the patients

with PCOS [28, 29]. In our study, serum leptin levels of the group with PCOS were higher (statistically significant) than the control group and leptin positively correlated with hyperinsulinemia and IR.

From the point of clinical use of CRP, fibrinogen, leptin, and adiponectin, considering the relationship of CRP and fibrinogen with inflammation, CRP may be useful to assess the risk of developing cardiovascular disease as supported by previous studies [14]. In young PCOS patients, the use of these markers is important for the clinical diagnosis of cardiovascular diseases that may develop in the long term. Since cardiovascular diseases are reversible before vascular damage occurs, they may be used as early markers in applying cardiovascular risk information to the clinical management of PCOS, especially non-pharmacological preventions like exercise and a healthy lifestyle [30]. It was also thought that CRP and Fibrinogen levels may help in finding women with subclinical atherosclerosis [31]. It has also been suggested that fibrinogen can be used as an early phase laboratory marker for biomarker screening in clinical practice [31]. Leptin increase and decrease of adiponectin, the other binary marker, is evident in obese and weak women with PCOS with variable degree of insulin resistance [18, 31]. It has been suggested that these two markers may be better markers for obesity, IR, coronary artery disease, and stroke [32]. Low adiponectin levels are independent risk factors for the development of metabolic syndrome and type 2 diabetes in the future [33]. In women with PCOS, changes in these two marker values, the first encounter with symptoms, and seeking medical help usually occur during adolescence. Thanks to the findings of this period (leptin increase, adiponectin decrease), it will be possible to take pharmacological and/or non-pharmacological preventions against early health risks such as obesity, type 2 diabetes, dyslipidemia, hypertension and possibly cardiovascular disease. However, we think that the findings in the clinical use of CRP, Fibrinogen, leptin, and adiponectin are limited, and many more studies are needed.

In conclusion, CRP and fibrinogen (cardiovascular risk markers) increase in women with PCOS, and both parameters were found to correlate with hyperinsulinemia and IR. In the patients with PCOS, decreased levels of adiponectin negatively correlated with IR and hyperinsulinemia as well as an increased level of leptin correlated with increased hyperinsulinemia. It may be interpreted such that they may play a role in the pathophysiology of PCOS.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical Approval This study was approved by The Ethics Committee of Yüzüncü Yıl University Medical Faculty (January 15 2009-TF).

Informed Consent All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration of 1975, as revised in 2000 Informed consent was obtained from all individual participants included in the study.

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About the Author

Dr. Cagdas Ozgokce studied as a student at Atatürk University Medical Faculty between 1996 and 2002, Erzurum, Turkey. Between 2005 and 2010, he specialized in obstetrics and gynecology department of YYÜ University Medical Faculty. Between 2011 and 2012 he worked as a specialist in obstetrics and gynecology department of University of Health Van Training and Research Hospital, Van, Turkey. He has been working as a specialist at obstetrics and gynecology department of Private Van Akdamar Hospital since 2013, Van, Turkey. His areas of interest are gynecologic oncology and endoscopy.