Endocr (2011) 39:272–277
DOI 10.1007/s12020-011-9437-6

ORIGINAL ARTICLE

Cardiovascular disease risk characteristics of the main polycystic ovary syndrome phenotypes

Berna Dilbaz · Enis Özkaya · Mehmet Cinar · Evrim Cakir · Serdar Dilbaz

Received: 13 January 2011 / Accepted: 2 February 2011 / Published online: 10 March 2011

Abstract The aim of this article was to evaluate the clinical, endocrine, and cardiovascular disease risk profile differences among main polycystic ovary syndrome (PCOS) phenotypes. One hundred and thirty-nine consecutive women were included in the study. Body mass index (BMI), serum follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, estradiol, testosterone, dehydroepiandrosterone sulfate, fasting glucose, low density lipoprotein (LDL-C), total cholesterol, high density lipoprotein (HDL-C) high sensitive CRP, c-peptide, insulin, insulin sensitivity and carotid intima thickness were compared among different phenotype groups of PCOS: Group 1—PCO (polycystic ovaries)-anovulation ($n = 34$), Group 2—Hyperandrogenemia (HA)-anovulation ($n = 30$), Group 3—HA-PCO ($n = 32$), and Group 4—HA-PCO-anovulation ($n = 43$). Statistically significant differences among the different phenotype groups in terms of waist hip ratio, total cholesterol, LH, estradiol, fasting glucose, progesterone, free testosterone, and carotid intima media thickness were observed. The lowest mean CIMT was observed in Group 3, and the highest fasting glucose levels were in Group 4, while the lowest mean free testesterone was measured in Group 1. BMI, LDL-C, and total cholesterol showed significant positive correlations with CIMT ($r = 0.411$, $P = 0.001$; $r = 0.258$, $P = 0.006$; $r = 0.199$, $P = 0.033$). The lowest LDL-C, total cholesterol, and BMI were found in Group 3, but differences were not statistically significant. High-sensitive CRP levels were similar among the groups ($P = 0.103$). Group 3 PCOS with PCO and hyperandrogenemia phenotype has lower cardiovascular disease risk compared to other phenotypes.

Keywords Polycystic ovary syndrome · Carotid intima media thickness · Cardiovascular disease risk

This study compared four different types of PCOS phenotypes in terms of metabolic, endocrine and cardiovascular risk factors. Ovulatory patients with hyperandrogenemia and polycystic ovaries have lower cardiovascular risk factors compared to others.

B. Dilbaz · M. Cinar · S. Dilbaz
Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Maternity & Women's Health Teaching and Research Hospital, Ankara, Turkey

E. Özkaya (✉)
Department of Obstetrics and Gynecology, Dr. Sami Ulus Women's Health Teaching and Research Hospital, Demetevler 10. sok. 63/15, Yenimahalle, Ankara, Turkey
e-mail: enozkaya1979@gmail.com

E. Cakir
Department of Endocrinology and Metabolism, Diskapı Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey

Introduction

Polycystic ovary syndrome (PCOS) is a multifactiorial and polygenic pathology that manifests itself with a wide spectrum of signs and symptoms that are related to the disturbances of reproductive, endocrine, and metabolic functions at various degrees resulting in a heterogenous presentation of the disease [1]. The diagnostic criteria for (PCOS) has undergone several changes in recent years. While the clinical presentation of chronic anovulation and hyperandrogenism has been stressed as the major diagnostic criteria [2], the presence of normal ovulatory function in women with PCOS has been acknowledged in recent years [3–5]. New diagnostic criteria were established in 2004, placing all these three factors: presence of chronic anovulation, hyperandrogenism, and polycystic

ovaries together, with a special emphasis placed on existence of polycystic ovaries on ultrasonography [6, 7]. PCOS was diagnosed in the presence of two of the three diagnostic criteria. Using these criteria, PCOS manifests itself in four different phenotypes: hyperandrogenism (clinical or biochemichal) and chronic anovulation; hyperandrogenism and polycystic ovaries but with ovulatory cycles; and chronic anovulation and polycystic ovaries without clinical hyperandrogenism and hyperandrogenism, chronic anovulation and polycystic ovaries.

PCOS is associated with a higher risk of diabetes, hypertension, dyslipidemia, metabolic syndrome, endothelial dysfunction, and cardiovascular disease [8]. There are studies showing the association between subclinical atherosclerosis, vascular dysfunction, and PCOS. These studies has shown the reduced vascular compliance and vascular endothelial dysfunction in some of the patients with PCOS [9–12]. Measurement of carotid intimal thickness (CIMT), a noninvasive vascular evaluation of atherosclerotic plaque is a valuable tool for evaluation of cardiovascular disease risk in patients with PCOS as increase in CIMT is associated with cardiovascular events, mainly stroke [13]. The aim of this study was to determine the clinical significance of PCOS diagnostic criteria in terms of cardiovascular disease risk by CIMT measurement.

Methods and materials

A total of 139 consecutive women with PCOS underwent the screening investigation at the Infertility Department of Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital between September 2009 and March 2010. Subjects were selected without intention to balance groups. Sample size was calculated with 95% CI and 80% power according to the previous study by Guestella et al. [14]. All the women presenting with one or two or all of the following complaints: oligomenorrhoea, hirsutism and infertility were systematically evaluated in our outpatient clinic. In the systematic evaluation, all the participants underwent sonographic evaluation and were screened for hormonal abnormalities and insulin resistance. Standardized screening was approved by the local Institutional Review Board, and signed written informed consent was obtained from all of the participants. According to the Rotterdam (ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) criteria, PCOS was diagnosed when at least two of the following criteria were present: oligo/amenorrhea, clinical or biochemical hyperandrogenism, and PCO on ultrasonography. Paitents with other etiologies mimicking PCOS, like cushing syndrome, late-onset adrenal hyperplasia or androgen-producing neoplasm, and thyroid dysfunction or hyperprolactinemia were considered as exclusion criteria. Patients who had taken any medication during the previous 3 months were excluded from the study. Anovulation was ruled out, based on day-3 FSH and estradiol (E2) assessment with day-21 progesterone level. Anovulation was defined as having a serum progesterone of <3 ng/ml on day 21–24 of the menstrual cycle. Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman–Galwey score ≥ 8) [15] and/or acne and/or alopesia. Polycystic ovary morphology was established using the criteria of ten or more peripheral follicular cysts 8 mm in diameter or less in one plane along with increased central ovarian stroma based on the Rott-PCOS criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

Medical history regarding age, race, menstrual cycle pattern, personal and family medical history, any previous or current use of medication, the presence of acne, and hirsutism were recorded. Menstrual cycle length shorter than 24 days and longer than 34 days were recorded as abnormal. Oligomenorrhea was diagnosed in patients with cycles higher than 35 days intervals, and amenorrhea was determined in the absence of menstruation in 6 months duration.

Body mass index (BMI), waist, and hip circumferences were recorded. Fasting early morning endocrine profile (including pituitary hormones, ovarian, and adrenal steroids), serum lipids, glucose, and insulin levels were measured in the follicular phase of a spontaneous or progesterone-induced menstrual cycle. Progesterone levels were measured at 21st day of the cycle.

Waist circumference was measured at the narrowest level between the costal margin and iliac crest, and the hip circumference was measured at the widest level over the buttocks while the subjects were standing and breathing normally. The waist-to-hip ratio (WHR) was calculated.

Hirsutism was established by using the Ferriman–Gallwey score. The BMI, WHR, and hirsutism scores were assessed by a single investigator for all of the subjects.

Transvaginal ultrasonography was systematically performed by the same investigator using the 7.5 MHz transvaginal probe to a logic ultrasound system. Antral follicles were measured in three dimensions, and those with a mean diameter of 2–9 mm counted.

High-resolution B-mode ultrasound images of the right common carotid artery were obtained with a 7.5 MHz linear array transducer attached to a logic ultrasound system. Subjects were placed in a supine position with the head rotated to the left using a 45° head block. The jugular vein and carotid artery were located in the transverse view with the jugular vein stacked above the carotid artery. The transducer was then rotated 90° around the central line of the transverse image of the stacked jugular vein–carotid artery to obtain a longitudinal image while maintaining the

vessels in the stacked position. The distal common carotid arterial far wall IMT was measured by the radiologist who was blinded to the laboratory findings and PCOS phenotype group of the patient.

Plasma glucose was determined by glucose oxidase/peroxidase method (Gordion Diagnostic, Ankara, Turkey). Serum levels of follicle-stimulating hormone, luteinizing hormone (LH), prolactin, dehydroepiandrosterone sulfate (DHEAS), total testosterone (T), insulin, cortisol, and thyroid stimulating hormone (TSH) were measured with specific electrochemiluminescence immunoassays (Elecsys 2010 Cobas, Roche Diagnostics, Mannheim, Germany). Serum levels of 17 hydroxyprogesterone and free testosterone were measured by radioimmunoassay. Levels of total-cholesterol, high-density lipoprotein (HDL-C) cholesterol, and triglyceride (TG) were determined with enzymatic colorimetric assays by spectrophotometry (BioSystems S.A, Barcelona (Spain)). Low-density lipoprotein (LDL-C) cholesterol was calculated using the Friedewald formula.

Serum c-reactive protein (CRP) was determined using high-sensitive CRP (hsCRP) immunonephelometry (BN, Dade-Behring; Marburg, Germany).

Insulin resistance was calculated using the homeostatic model assessment insulin resistance index (HOMA-IR) according to the formula, HOMA-IR: fasting plasma glucose (mmol/l) × fasting serum insulin (mU/ml)/22.5 [16]. Biochemical hyperandrogenemia was accepted as the free testosterone levels higher than 3.2 pg/ml according to the upper level of normal range in our laboratory.

Statistical analysis was performed by the principal investigator using the Statistical Package for the Social Sciences, version 11.0 (SPSS, Inc., Chicago, Illinois) Four different phenotypes were defined as follows: Group 1—PCO-anovulation, Group 2—Hyperandrogenemia (HA)-anovulation, Group 3—HA-PCO(ovulatory PCOS), and Group 4—HA-PCO-anovulation. The group means were compared using analysis of variance (ANOVA) with post-hoc least squares means pairwise comparisons (after log transformation of the values). Correlation analysis was used for showing way associations. All data are presented as mean ± standard deviation (SD). Data were considered significant at $P \leq 0.05$.

Results

Out of the 139 patients who were diagnosed to have PCOS, 34 (24.4%) were in Group 1, 30 were in Group 2 (21.5%), while 32 (23.1%) were in Group 3 and 43 (30.9%) had anovulation accompanied with hirsutism and polycystic ovaries (Group 4). Group characteristics were shown in Table 1.

Group comparisons

There were statistically significant differences among the four phenotype groups in terms of WHR, total cholesterol, LH, estradiol, fasting glucose, progesterone, f-T, and CIMT (Table 2). The lowest CIMT levels were observed in group 3 (p:0.001, p:0.001, p:0.009) (Fig. 1). The lowest LDL-C, total cholesterol, and BMI were in group 3 but differences were not statistically significant. Hs-CRP levels were similar in between the groups (p:0.103). Mean values of metabolic and endocrine parameters of different phenotypes were shown with patient characteristics in Table 2. Group differences of CIMT were shown in Fig. 1. Subjects with and without biochemical HA were compared on CIMT and found to be similar (0.44 vs. 0.41 mm, $P = 0.121$, respectively). Other parameters were evaluated between subjects with and without biochemical HA, and groups were found to be similar ($P > 0.05$).

Correlations

Both BMI and WHR were positively correlated with age ($r = 0.251$, $P = 0.012$; $r = 0.251$, p:0.004). LDL-C level and BMI were positively correlated ($r = 0.196$, $P = 0.025$) while HDL-C was significantly negatively correlated with WHR ($r = -0.190$, $P = 0.03$). Correlation coefficient between age and total cholesterol was $r = 0.317$ ($P = 0.001$). BMI, LDL-C, and total cholesterol showed

Table 1 Patient characteristics of different phenotypes

	Group1 PCO-AO $n = 34$	Group2 HA-AO $n = 30$	Group3 HA-PCO $n = 32$	Group4 HA-AO-PCO $n = 43$	P value
Age (years)	24.35 ± 5.01	24.46 ± 5.08	25.26 ± 6.43	23.22 ± 5.94	0.481
Parity	1.76 ± 0.65	1.59 ± 0.55	1.60 ± 0.56	1.62 ± 0.57	0.606
BMI (kg/m^2)	24.44 ± 4.08	24.73 ± 5.19	23.58 ± 5.13	24.04 ± 3.62	0.770
WHR	0.74 ± 0.06	0.77 ± 0.06	0.77 ± 0.06	0.80 ± 0.06	0.004
FG Score	2.5 ± 0.66	13.15 ± 3	13.36 ± 2.61	13.51 ± 2.54	0.001

Table 2 Endocrine and metabolic characteristics of different phenotypes

	Group1 PCO-AO $n = 34$	Group2 HA-AO $n = 30$	Group3 HA-PCO $n = 32$	Group4 HA-AO-PCO $n = 43$	P value
LDL-C (mg/dl)	113.84 ± 31.32	113.29 ± 32.05	93.01 ± 33.71	94.86 ± 31.62	0.08
Trigliserid (mg/dl)	112.96 ± 81.25	100.64 ± 46.52	91.40 ± 48.39	107.16 ± 68.02	0.271
HDL-C (mg/dl)	60.96 ± 38.27	52.93 ± 13.29	53.84 ± 15.36	55 ± 10.94	0.466
Cholesterol (mg/dl)	191.48 ± 36.32	182.38 ± 38.71	165.59 ± 42.33	170.69 ± 42.72	0.05
FSH (mIU/ml)	5.07 ± 2.11	4.85 ± 1.72	5.86 ± 3.36	5.70 ± 2.57	0.323
LH (mIU/ml)	10.75 ± 6.80	11.94 ± 7.34	7.45 ± 4.78	7.08 ± 5.41	0.003
Estrodiol (mIU/ml)	64.46 ± 51.31	100.56 ± 78.28	116.66 ± 83.16	69.33 ± 92.26	0.027
DHEA_S (μgr/dl)	270.29 ± 161.41	277.53 ± 99.38	235.84 ± 141.61	270.20 ± 140.52	0.692
Fasting glucose (mg/dl)	83.52 ± 8.94	86.25 ± 11.62	90.25 ± 11.81	94.52 ± 12	0.001
f-T (pg/ml)	0.75 ± 0.64	3.11 ± 1.31	2.51 ± 0.87	2.53 ± 1.19	0.001
CIMT (mm)	0.45 ± 0.08	0.45 ± 0.08	0.36 ± 0.07	0.41 ± 0.06	0.001
Insulin (μiu/ml)	11.54 ± 6.49	10.80 ± 5.48	10.85 ± 4.01	17.39 ± 20.86	0.104
C-peptide (ng/ml)	2.99 ± 1.33	2.87 ± 2.12	2.22 ± 0.59	2.66 ± 1.72	0.299
Hs-CRP (mg/l)	0.70 ± 1.36	1.22 ± 1.96	1.70 ± 1.99	2.60 ± 4.77	0.103
HOMA-IR	2.55 ± 1.57	2.31 ± 1.10	2.40 ± 0.94	3.98 ± 4.63	0.59
Progesteron (ng/ml)	2.63 ± 3.25	1.84 ± 4.12	4.34 ± 4.69	1.19 ± 2.96	0.007
Systolic TA (mmHg)	102.5 ± 8.5	101.9 ± 7.4	101.7 ± 8.3	101.6 ± 7.9	0.966
Diastolic TA (mmHg)	72.5 ± 10.5	71.1 ± 9.2	71.3 ± 9.5	71.9 ± 9.7	0.936

AO Anovulation, *BMI* body mass index, *WHR* Waist/ratio, *FG score* Ferrimann Galoway score, *f-T* free testesterone, *TA* tension arterial

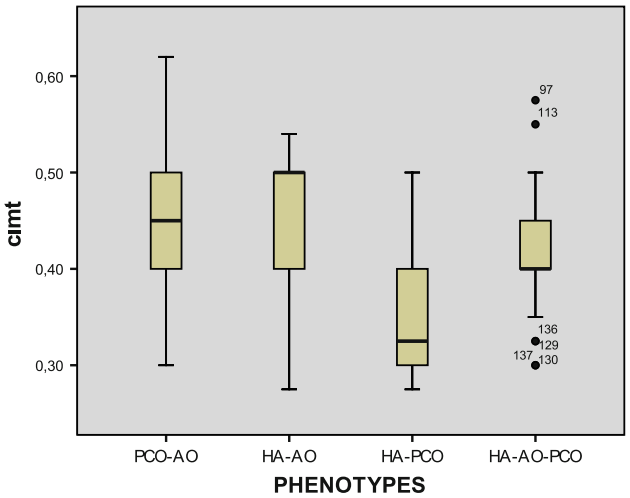

Fig. 1 CIMT in different PCOS phenotypes. *CIMT* Carotid intima media thickness

significant positive correlation with CIMT ($r = 0.411$, $P = 0.001$; $r = 0.258$, $P = 0.006$; $r = 0.199$, $P = 0.033$). OGTT results and WHR were also correlated ($r = 0.402$, $P = 0.003$). Multivariate regression analyses revealed an association between BMI ($P < 0.001$), PCOS phenotype ($P = 0.004$), and CIMT (Statistically significant variables in correlation analysis were included in the model).

WHR, BMI, f-T, fasting glucose, LDL-C, and total cholesterol-adjusted mean CIMT differences among groups remained significant ($P < 0.001$).

Discussion

The heterogenity of the signs and symptoms of PCOS had led to description of four phenotypes according to three diagnostic criteria. The clinical, hormonal, and metabolic parameters of these phenotypes have been a subject of interest to identify specific risk groups related to the them and to specify the most risky phenotypes [15].

Guastella et al. reported relative prevalence of different phenotypes among 206 patients with PCOS, and 53.9% of the patients were in group 4, while only 8.9% of the patients had hyperandrogenism and anovulation with normal ovaries (Group 2), and 28.8% of the cases were found to have ovulatory PCOS (Group 3) [14]. Out of the 139 patients diagnosed to have PCOS in our series, a majority (30.9%) had all the three characteristics (Group 4) of the Rotterdam guidelines. Only 23% of the patients had ovulatory PCOS (Group 3). The normoandrogenic PCOS cases (Group 1) constituted 24.4% of our patient group, while 21.5% exhibited hyperandrogenism and anovulation with normal ovaries (Group 2).

In this study, different patient groups diagnosed to have PCOS were analyzed, and the heterogenity of the disease has been demonstrated. Wiltgen et al. reported a remarkably higher HOMA-IR in the classic PCOS phenotype group in comparison to a group of ovulatory women with hirsutism, normal androgen levels, and polycystic ovaries, and to a group with isolated hirsutism with normal ovaries and androgen levels [15]. Their study demonstrated that hyperandrogenism and ovulatory dysfunction with or without PCOS is associated with worse metabolic profile and higher insulin resistance compared to other groups and hirsute ovulatory patients with PCOS, but with normal androgen levels, it had the lowest prevalence of cardiovascular risk factors. The authors implied that hyperandrogenism could be a key factor responsible for metabolic changes, as a moderate correlation was shown between androgen levels and insulin resistance markers like HOMA-IR and lipid accumulation product index.

Cardiovascular disease risk was evaluated in this study by CIMT measurements in different PCOS phenotypes and the lowest CIMT values were observed in group 3 ovulatory PCOS patients; other three phenotypes were found to have similar CVD risk. CVD risk was significantly associated with high LDL-C, total cholesterol levels and BMI. The lowest mean LDL-C, total cholesterol levels, and BMI were observed in group 3 too. Mean estradiol level was higher in Group 3; protective effect of this high estradiol levels needs further investigations. These data imply that ovulatory women with hyperandrogenism and polycystic ovaries have the lowest CVD risk, and anovulation has the major negative effect on CVD risk. In all the phenotypes in this study group, means of CIMT were lower than cut off, which was thought to be due to young age of study population. Guastella et al. evaluated clinical and endocrine parameters of the main PCOS phenotypes in their recent study and described ovulatory PCOS as a milder form of the disease [14]. Contrary to a recently published study by Luque-Ramiez et al. [17], which relate increased CIMT with androgen excess in women with PCOS, in this study, the patients with ovulation but hyperandrogenism and polycystic ovaries (Group 3) had lower CIMT compared to anovulatory women without hyperandrogenism (Group1). However, in their study, ovarian morphology was not evaluated, and therefore their results could not be reflected on normoandrogenic anovulatory women with PCOS.

In a study by Rizzo et al., which compared ovulatory forms of PCOS with anovulatory phenotype, ovulatory women with PCOS showed milder forms of atherogenic dyslipidemia than anovulatory PCOS [18].

However, the nonhyperandrogenic Group 1 phenotype (Oligo-anovulatory gorup with polycystic ovaries) may represent a form of PCOS with an intermediate or milder metabolic risk profile.

Androgen excess appears to participate the metabolic and cardiovascular changes as an independent parameter, in women with PCOS and is proposed to be directly related to the increased incidence of coronary artery disease and of cardiovascular events [19, 20]. We have compared the parameters between subjects with and without biochemical HA, and the two groups were found to be similar.

Subclinical atherosclerosis was compared between healthy subjects with regular menses and PCOS patients and PCOS was not found to be associated with atherosclerosis determined by coronary artery calcium and aortic plaque [21].

A small–sized sample study has been conducted to assess biochemical and clinical risk factors for cardiovascular disease, and PCOS was found to be associated with the defined risk factors [22]. These contraversies may be explained by the heterogenity of the diagnosis. Recent discussions were based on the diagnostic criterias for PCOS, and hyperandrogenemia is thought to be major diagnostic criteria. New criteria have been suggested, and further studies are needed to compare phenotypes according to these criteria [23].

The available data so far indicate that coronary heart disease, as well as cerebrovascular disease is more common in postmenopausal PCOS patients. Persisting high androgen levels through the menopause, obesity, and maturity onset diabetes mellitus are proposed as the main mechanisms accounting for the increased risk [24]. In this study, the chronic anovulation was found to be the mechanism for increased risk rather than HA.

Small size of this sample is the major disadvantage of this study; another disadvantage is the low BMI and early age of study population. This study tried the show the heterogenity of phenotypes and demonstrate the future coronary disease risk among groups.

The different phenotypes of PCOS exhibit similarities within the same group and differ from each other in terms of endocrine and metabolic parameters. It is important to identify the groups carrying a higher risk in terms of cardiovascular outcome to design a screening and follow-up program for them. Although increased incidence of metabolic abnormalities and metabolic diseases like type 2 diabetes, and several cardiovascular abnormalities have been widely demonstrated in PCOS, larger and multicenter trials with a long-term follow-up period are required to define the incidence of cardiovascular risk and cardiovascular disease and cardiovascular outcome in patients with PCOS in the context of the presence of the three diagnostic criteria. The contraverseries in the results of the published studies from the literature might well be related to nonrecognition and underestimation of the individual CVD risk factors that might alter the whole scenario.

References

1. L.J. Rajashekar, D. Krishna, M. Patil, Polycystic ovaries and infertility: our experience. Hum. Reprod. Sci. **1**(2), 65–72 (2008)
2. J.K. Zawdaki, A. Dunaif, Diagnostic criteria for polycystic ovary syndrome: toward a rationale approach, in *Polycystic ovary syndrome*, ed. by A. Dunaif, J.R. Givens, F. Haseltine, G.R. Merriam (Blackwell Scientific Publications, Boston, 1992), pp. 377–384
3. E. Carmina, R.A. Lobo, Do hyperandrogenic women with normal menses have polycystic ovary syndrome? Fertil. Steril. **71**, 319–322 (1999)
4. E. Carmina, R.A. Lobo, Polycystic ovaries in women with normal menses. Am. J. Med. **111**, 602–606 (2001)
5. J.R. Chang, Polycystic ovary syndrome: diagnostic criteria, in *Polycystic ovary syndrome*, ed. by R.J. Chang, J.J. Heindel, A. Dunaif (Marcel Dekker, New York, 2002), pp. 361–365
6. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. Fertil. Steril. **81**, 19–25 (2004)
7. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. Hum. Reprod. **19**, 41–47 (2004)
8. A. Dokras, Cardiovascular disease risk factors in polycystic ovary syndrome. Semin. Reprod. Med. **26**(1), 39–44 (2008)
9. E.O. Talbott, J.V. Zborowski, J.R. Rager, M.Y. Boudreaux, D.A. Edmundowicz, D.S. Guzick, Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. **89**, 5454–5461 (2004)
10. R.C. Christian, D.A. Dumesic, T. Behrenbeck, A.L. Oberg, P.F. Sheedy 2nd, L.A. Fitzpatrick, Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. **88**, 2562–2568 (2003)
11. C.J.G. Kelly, A. Speirs, G.W. Gould, J.R. Petrie, H. Lyall, J.M.C. Connell, Altered vascular function in young women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. **87**, 742–746 (2002)
12. G. Paradisi, H.O. Steinberg, A. Hempfling, J. Cronin, G. Hook, M.K. Shepard, A.D. Baron, Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation **103**, 1410–1415 (2001)
13. C.J. Alexander, E.P. Tangchitnob, N.E. Lepor, Polycystic ovary syndrome: a major unrecognized cardiovascular risk factor in women. Rev. Obstet. Gynecol. **2**(4), 232–239 (2009)
14. E. Guastella, R.A. Longo, E. Carmina, Clinical and endocrine characteristics of the main polycystic ovary syndrome phenotypes. Fertil. Steril. **94**(6), 2197–2201 (2010)
15. D. Wiltgen, P.M. Spritzer, Variations in metabolic and cardiovascular risk in women with different polycystic ovary syndrome phenotypes. Fertil. Steril. **94**(6), 2493–2496 (2010)
16. R.S. Legro, V.D. Castracane, R.P. Kauffman, Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet. Gynecol. Surv. **59**(2), 141–154 (2004)
17. M. Luque-Ramírez, C. Mendieta-Azcona, F. Alvarez-Blasco, H.F. Escobar-Morreale, Androgen excess is associated with the increased carotid intima-media thickness observed in young women with polycystic ovary syndrome. Hum. Reprod. **22**(12), 3197–3203 (2007)
18. M. Rizzo, K. Berneis, M. Hersberger, I. Pepe, G. Di Fede, G.B. Rini, G.A. Spinas, E. Carmina, Milder forms of atherogenic dyslipidemia in ovulatory versus anovulatory polycystic ovary syndrome phenotype. Hum. Reprod. **24**(9), 2286–2292 (2009)
19. J.C. Lovejoy, G.A. Bray, M.O. Bourgeois, R. Macchiavelli, J.C. Rood, C. Greeson, C. Partington, Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women—a clinical research center study. Clin. Endocrinol. Metab. **81**(6), 2198–2203 (1996)
20. C.D. Christakou, E. Diamanti-Kandarakis, Role of androgen excess on metabolic aberrations and cardiovascular risk in women with polycystic ovary syndrome. Womens Health **4**(6), 583–594 (2008)
21. A.Y. Chang, C. Ayers, A. Minhajuddin, T. Jain, P. Nurenberg, J.A. De Lemos, R.A. Wild, R.J. Auchus, Polycystic ovarian syndrome and subclinical atherosclerosis among women of reproductive age in the Dallas heart study. Clin. Endocrinol. **74**(1), 89–96 (2010)
22. A. Karaer, S. Cavkaytar, I. Mert, U. Buyukkagnici, S. Batioglu, Cardiovascular risk factors in polycystic ovary syndrome. J. Obstet. Gynaecol. **30**(4), 387–392 (2010)
23. R. Azziz, E. Carmina, D. Dewailly, E. Diamanti-Kandarakis, H.F. Escobar-Morreale, W. Futterweit, O.E. Janssen, R.S. Legro, R.J. Norman, A.E. Taylor, S.F. Witchel, Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society, The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil. Steril. **91**(2), 456–488 (2009)
24. I. Lambrinoudaki, Cardiovascular risk in postmenopausal women with the polycystic ovary syndrome. Maturitas **68**(1), 13–16 (2010)