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Body Mass Index below Obesity Threshold Implies Similar Cardiovascular Risk among Various Polycystic Ovary Syndrome Phenotypes

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Abstract
Objective: The aim of this study was to determine the cardiometabolic risk factors in different polycystic ovary syndrome (PCOS) phenotypes. ***Subjects and Methods:*** This cross-sectional study was performed between 2010 and 2011. Eighty-nine patients with PCOS and 25 age- and weight-matched healthy controls were included in the study. Patients were grouped using the Rotterdam 2003 criteria as: group 1, oligomenorrhea and/or anovulation (ANOV) and hyperandrogenemia (HA) and/or hyperandrogenism (n = 23); group 2, ANOV and polycystic ovaries (PCO; n = 22); group 3, HA and PCO (n = 22); group 4, ANOV, HA and PCO (n = 22); group 5, controls (n = 25). Laboratory blood tests for diagnosis and cardiometabolic risk assessments were performed. Insulin resistance (IR) was calculated in all patients with the homeostasis model assessment of IR (HOMA-IR) formula. An euglycemic hyperinsulinemic clamp test was performed on 5 randomly selected cases in each subgroup, making 25 cases in total, and indicated as the 'M' value (mg/kg/min), which is the total body glucose disposal rate. ***Results:*** The mean BMI values of the groups were: group 1, 26.1 ± 5.3; group 2, 27.9 ± 5.2; group 3, 24.3 ± 4.2; group 4, 27.9 ± 7.5; group 5, 24.7 ± 5.2 ($p > 0.05$). There were no differences in the lipid profile, plasma glucose, HOMA-IR, insulin and M values between the groups ($p > 0.05$). Phenotypes with oligomenorrhea/anovulation (groups 1, 2 and 4) were more obese than group 3 ($p = 0.039$). ***Conclusions:*** The cardiometabolic risk profile was similar among the PCOS subgroups. This finding could be attributed to the mean BMI values, which, being below 30, were not within the obesity range. Obesity appeared to be an important determinant of high cardiovascular risk in PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder characterized by a cluster of major cardiovascular (CV) risk factors. Insulin resistance (IR) is regarded as a key feature of PCOS. The association between IR and glucose metabolic disorders, such as impaired glucose tolerance, type 2 diabetes and CV disease, has been reported [1, 2]. The findings indicated that women with PCOS and IR are at high risk of metabolic disorders. Of equal importance, Boudreaux et al. [3] reported a 5-fold increased risk of type 2 diabetes among women with PCOS after 8 years

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of follow-up [3]. Although there are conflicting reports, the risk of diabetes is claimed to occur independently of obesity, and may be worsened by obesity [3–5]. It has been observed that abdominal obesity and PCOS interact to promote premature atherosclerosis and increase CV mortality [6].

In 1992, the National Institutes of Health (NIH) proposed a diagnostic criteria [7] concentrating primarily on hyperandrogenism and anovulation for PCOS. After excluding all other etiological causes, the NIH criteria required the presence of oligo-/anovulation and hyperandrogenemia/hyperandrogenism. In 2003, in Rotterdam, the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) formulated a new set of criteria which added two new phenotypes – hyperandrogenic ovulatory and nonhyperandrogenic anovulatory women – to the spectrum of the syndrome [8]. The Rotterdam 2003 criteria are now used worldwide for the diagnosis of PCOS; however, it has not been clarified whether or not various PCOS phenotypes carry different CV risk profiles.

Although patients with full-blown PCOS are supposed to carry the worst CV risk profile, studies comparing different phenotypes demonstrate various results [9–12]. Body mass index (BMI) and plasma insulin have been reported to be higher in PCOS patients with oligo-/amenorrhea and hyperandrogenemia/hyperandrogenism compared to the ones with hyperandrogenemia/hyperandrogenism and polycystic ovaries (PCO) [10–12]. Irregular menstrual cycles have been associated with an increased risk for CV mortality [13]. Also, amenorrhea has been demonstrated to accompany a more pronounced IR than oligomenorrhea and polymenorrhea [14]. In the present study, we investigated whether or not traditional CV risk profiles differed among various nonobese PCOS patients diagnosed according to Rotterdam 2003 criteria.

Subjects and Methods

This cross-sectional study was performed at the outpatient endocrinology clinic of Baskent University Faculty of Medicine, Adana Hospital, and eligible patients were recruited between February 2010 and June 2011. Eighty-nine newly diagnosed PCOS patients and 25 age- and weight-matched healthy controls were included in the study. The exclusion criteria were current smoking, chronic heavy alcohol consumption, severe obesity (BMI >35), accompanying chronic kidney or liver disease or malignancy, any chronic metabolic disease such as diabetes and hypertension, etc., and any chronic medication use.

The diagnosis of PCOS was performed according to the Rotterdam 2003 criteria [8] requiring copresentation of at least two of oligomenorrhea and/or anovulation (ANOV), hyperandrogenemia and/or hyperandrogenism (HA), and/or PCO at ultrasonographic examination. The 89 patients were divided into the following subgroups: group 1, ANOV and HA (n = 23); group 2, ANOV and PCO (n = 22); group 3, HA and PCO (n = 22); group 4, ANOV, HA and PCO (n = 22); group 5, healthy controls (n = 25). Cases admitted with the complaint of hirsutism but who after diagnostic work-up did not provide sufficient criteria for PCOS were included in the control group; all had ovulatory cycles.

Euglycemic hyperinsulinemic clamp (EHC) was performed on 25 randomly selected cases and the results were recorded as the M value (mg/kg/min) [15]. The total number of the participants in the subgroups and the number of cases subjected to EHC in each subgroup, respectively, were: group 1, 23 and 5; group 2, 22 and 4; group 3, 22 and 6; group 4, 22 and 5; group 5, 25 and 5.

The PCOS patients were also separated into two groups regarding their menstrual state – those with ANOV (groups 1, 2 and 4; ANOV positive, n = 67) and those without ANOV (group 3; ANOV negative, n = 22). The cardiometabolic risks between these groups were compared.

Study Protocol

The study protocol was approved by the Institutional Ethics Committee. Each participant gave written informed consent, their medical history was taken, a physical examination was performed and their BMI was calculated as body weight (kg)/height $(m)^2$. Measurements were made early in the morning following urination with an empty stomach and with light clothing using the Seca model 220 digital device (Seca, Hamburg, Germany). Obesity was determined as a BMI threshold of >30 [16]. Hirsutism was defined as a modified Ferriman-Gallwey score equal to or higher than 8 [17]. Menstruating patients between the 2nd to 5th days of their cycle and amenorrheic cases on any day were subjected to hormonal analyses for diagnosing PCOS. An oral glucose tolerance test (OGTT) with 75 g of glucose after 8–10 h of overnight fasting, following at least 3 days of a diet containing 300 g of carbohydrate, was performed on all subjects. Blood samples for glucose and insulin were obtained from the forearm vein at 0 min and for glucose only at 120 min of the test. The peripheral insulin sensitivity of the participants was calculated using the homeostasis model assessment of IR (HOMA-IR) formula: fasting venous glucose (mmol/l) × fasting insulin (mU/ml)/22.5 [18].

Serum follicle-stimulating hormone, luteinizing hormone (LH), estradiol, total testosterone, prolactin, thyroid-stimulating hormone and 17-OH progesterone, whole blood count, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein and triglyceride were measured simultaneously in early morning fasting serum samples. A randomly selected comparable number of participants were subjected to serum fibrinogen measurement (group1, 17; group 2, 17; group 3, 15; group 4, 19; group 5, 19).

Glucose and lipid measurements were performed using the colorimetric method, 17-OH progesterone levels were measured using ELISA and all other biochemical parameters were processed using the chemiluminescence microparticle immunoassay method, with a reference limit for total testosterone of 0.14–0.76 ng/ml. EHC as defined by DeFronzo et al. [15] was performed for detecting IR.

Table 1. Details of demographic features and hormonal findings of the participants performed for diagnosing PCOS

	Group 1: ANOV and HA (n = 23)	Group 2: ANOV and PCO (n = 22)	Group 3: HA and PCO (n = 22)	Group 4: ANOV, HA and PCO (n = 22)	Group 5: control (n = 25)	p
Age, years	24.2±5.9	23.4± 5.7	23.18±3.92	22.7±4.8	24.2±5.0	0.81
BMI	26.1±5.3	27.9±5.2	24.3±4.2	27.9±7.5	24.7±5.2	0.09
FSH, mIU/ml	4.3±1.4	4.1±1.6	4.4±0.8	4.7±1.2	4.9±1.4	0.22
LH, mIU/ml	5.0 (0.45–6.9)	5.7 (0.45–11.57)	4.6 (2.7–14.8)	6.4 (1.8–16.1)	3.4 (1.5–6.3)	0.024
E_2, pg/ml	34.9 (10–68)	40.4 (10–82)	40.2 (19–76)	45.0 (14–84)	37.1 (16–74)	0.24
Total testosterone, ng/ml	1.06±0.4	0.8±0.1	1.1±0.3	1.0±0.3	0.7±0.2	0.000
Prolactin, mIU/l	505 (145–2,903)	394.3 (117–888)	436.3 (142–1,020)	382.9 (164.6–1,166)	433.3 (100–747)	0.67

FSH = Follicle-stimulating hormone; E_2 = estradiol.

Table 2. List of parameters exhibiting a statistically significant difference between the study and control groups

	PCOS (n = 89)	Control (n = 25)	p
LH, mIU/ml	5.4 (0.5–16.6)	3.4 (1.5–6.3)	0.013
Total testosterone, ng/ml	1.0±0.3	0.7±0.2	0.004
pOGTT, mg/dl	106.5±22.4	94.1±18.3	0.013
Fibrinogen, g/l	3.3±0.6	3.0±0.5	0.025
Triglyceride, mg/dl	102.7 (30–363)	87.4 (29–305)	0.045

Values are the mean ± SD or median (minimum–maximum).

Statistical Analysis

The Statistical Package for the Social Sciences version 18.0 (SSPS Inc., Chicago, Ill., USA) was used for the statistical analyses. Categorical data were expressed as number and percentages, numeric data were expressed as the mean and standard deviation (SD) or as the median with the minimum and maximum range. Standard descriptive analysis, χ^2 test, independent samples t test and the Mann-Whitney U test were used where appropriate. Generalized linear models were used for the comparison of the study and control groups. A p value <0.05 was considered as statistically significant.

Results

There was no statistically significant difference among the groups regarding mean age (p = 0.081) and BMI values (group 1, 26.1 ± 5.3; group 2, 27.9 ± 5.2; group 3, 24.3 ± 4.2; group 4, 27.9 ± 7.5; group 5, 24.7 ± 5.2; p = 0.09). Hormonal analyses did not reveal significant differences among the groups, excluding total testosterone and LH. Groups 1, 3 and 4 had higher total testosterone than group 5, whereas groups 2 and 4 had higher LH than group 5 (p = 0.000 and 0.024, respectively; table 1). The PCOS group had statistically higher LH, total testosterone, post-OGTT 2nd hour plasma glucose (pOGTT), fibrinogen and triglyceride levels than the control group (p = 0.013, 0.004, 0.013, 0.025 and 0.045, respectively; table 2).

Analyses of cardiometabolic risk factors, including lipid profile, fasting plasma glucose, pOGTT, insulin, HOMA-IR and M values, revealed no statistically significant difference among the groups (p > 0.05), as shown in table 3. Regarding the ovulatory status of the patients, the ANOV-positive cases had a higher BMI (27.3 vs. 24.3, p = 0.039). However, their cardiometabolic risk factors exhibited a similar profile (p > 0.05).

Cardiometabolic risk factors were similar between the classical PCOS patients diagnosed according to the NIH 1990 criteria (groups 1 and 4) and the new phenotypes defined by the Rotterdam 2003 criteria (groups 2 and 3, p > 0.05; table 4).

Discussion

This cross-sectional study, which used the Rotterdam 2003 criteria in age- and weight-matched groups of PCOS phenotypes with mean BMIs below the obesity cutoff (BMI >30), demonstrated that nonobese phenotypes exhibited similar CV risk profiles. The M values obtained by EHC, which is the gold standard method for evaluating IR, were in accordance with the other cardiometabolic risk factors we studied.

Table 3. Comparison of the groups according to cardiometabolic risk factors

	Group 1: ANOV and HA (n = 23)	Group 2: ANOV and PCO (n = 22)	Group 3: HA and PCO (n = 22)	Group 4: ANOV and HA and PCO (n = 22)	Group 5: control (n = 25)	p
Total cholesterol, mg/dl	170.3±32.7	170.6±30.8	156.1±24.0	170.8±38.2	159.1±33.1	0.34
HDL cholesterol, mg/dl	42.1±10.2	45.2±9.3	44.5±8.3	51±11.5	47.4±15.3	0.10
LDL cholesterol, mg/dl	103.2±27.1	102.3±25.7	91.1±22.2	99.1±31.7	92.2±27.3	0.41
Triglycerides, mg/dl	113.8 (40–249)	102.9 (40–249)	93.0 (30–240)	100.6 (42–246)	87.4 (29–305)	0.67
Fibrinogen, g/l	3.4±0.5	3.4±0.6	3.4±0.5	3.2±0.8	3.0±0.5	0.19
FPG, mg/dl	86.3±7.02	90.6±8.3	87.0±5.7	90.7±7.6	89.3±8.2	0.16
pOGTT, mg/dl	104.7±25.4	110.7±22.4	104.6±19.2	106.2±23.0	94.1±18.3	0.12
Insulin, μIU/ml	12.2 (3.5–46)	13.4 (1.3–51)	9.6 (4.5–21.1)	12.3 (4.6–24.6)	8.7 (3.1–15.4)	0.18
HOMA-IR	2.6 (0.7–9.6)	3.0 (0.3–12.5)	2.0 (0.8–4.2)	2.7 (1.4–5.8)	1.9 (0.6–3.7)	0.14
M, mg/kg/min	4.5 (1.4–7.7)	4.8 (3.3–6.7)	4.8 (3.5–6.4)	3.7 (1.8–6.2)	4.9 (2.0–6.9)	0.84

Values are the mean ± SD or the median (minimum–maximum). HDL = High-density lipoprotein; LDL = low-density lipoprotein; FPG = fasting plasma glucose.

Table 4. Comparison of cardiometabolic risk profiles of classical PCOS patients diagnosed according to the NIH 1990 criteria and the new phenotypes defined by the Rotterdam 2003 criteria

	NIH 1990 (n = 45)	Rotterdam 2003 (n = 44)	p
Total cholesterol, mg/l	170.5±35.13	163.3±28.2	0.29
HDL cholesterol, mg/dl	46.5±11.7	44.8±8.76	0.45
LDL cholesterol, mg/dl	101.2±29.2	96.7±24.4	0.43
Triglycerides, mg/dl	107.4 (42–363)	98 (30–249)	0.47
FPG, mg/dl	88.5±7.5	88.8±7.3	0.83
pOGTT, mg/dl	105.4±24.0	107.7±20.8	0.63
Insulin, μIU/ml	12.2 (3.5–46.0)	11.5 (1.30–51.0)	0.89
HOMA-IR	2.6 (0.7–9.6)	2.5 (0.3–12.5)	0.83
M, mg/kg/min	4.1 (1.4–7.7)	4.8 (3.3–6.7)	0.40

Values are the mean ± SD or the median (minimum–maximum). NIH 1990 criteria patients: group 1 (ANOV and HA) + group 4 (ANOV, HA and PCO); Rotterdam 2003 criteria patients: group 2 (ANOV + PCO) + group 3 (HA + PCO). HDL = High-density lipoprotein; LDL = low-density lipoprotein; FPG = fasting plasma glucose.

The association between PCOS and CV risk factors has been identified in the literature [19–21]. Svendsen et al. [22] demonstrated that PCOS patients have higher 2nd hour glucose levels during an OGTT test than their non-PCOS peers. In a meta-analysis including 35 PCOS studies that investigated the syndrome's association with metabolic disorders (impaired glucose tolerance, type 2 diabetes and metabolic syndrome) PCOS cases were found to carry worse CV risk profiles [23]. Accordingly, our PCOS cases exhibited higher 2nd hour plasma glucose, fibrinogen and triglyceride levels. The differences regarding total testosterone and LH values among our groups were considered to result from the diagnostic criteria.

Studies analyzing the CV risk profiles of various PCOS phenotypes have focused on the negative impact of obesity and IR [9, 23, 24]. As is the case in type 2 diabetes, excessive adipose tissue is considered to play a crucial role in the development of PCOS. However, not all obese women, but rather those that are genetically vulnerable, progress to the syndrome. Obesity is claimed to cause more severe PCOS phenotypes from both a metabolic and reproductive point of view [25]. In a study by Ketel et al. [26], PCOS patients with central obesity demonstrated an increased arterial stiffness than their nonobese peers. Additionally, EHC was performed and lower M values were found in the obese PCOS cases included in that study. The authors concluded that insulin sensitivity decreases in parallel to increasing central adipose tissue in PCOS. In our study, the M values of the groups were not different and the mean BMl values were not within the obesity range. Our findings also pointed to the critical role of obesity in the development of the high CV risk profile of the syndrome.

In a previous study, Rizzo et al. [27] found that women with ovulatory PCOS have milder forms of atherogenic dyslipidemia than anovulatory PCOS. Using the Rotterdam 2003 criteria, another study succinctly showed that PCOS phenotypes with oligo-/anovulation and hyperandrogenism have more severe metabolic problems and

higher BMI values [9]. The positive correlation between HOMA-IR and BMI values in that study are considered as solid evidence for the worsening of PCOS symptoms with increasing fat tissue. Accordingly, the statistically insignificant difference in insulin sensitivity measures as well as other CV risk parameters among our PCOS phenotypes can be attributed to the similar mean BMI values, which were not within the obesity range.

The impact of oligo-/anovulation and/or hyperandrogenemia has been investigated on the CV risk profile of PCOS patients before. In some studies, oligo-/anovulation has been claimed to exert a stronger negative impact than hyperandrogenemia [24, 28]. Conversely, Mehrabian et al. [29] found the incidence of metabolic syndrome to be higher in oligo-/anovulatory and hyperandrogenemic PCOS cases than oligo-/anovulatory and normoandrogenemic subjects using the Rotterdam 2003 criteria. They concluded that hyperandrogenemia has the more powerful effect. In our study, oligo-/anovulatory PCOS cases clearly demonstrated higher BMI values. On the other hand, the statistically indifferent CV risk profiles between our ovulatory and oligo-/anovulatory groups were unexpected. Considering the relatively low mean BMI values of our groups, the link between CV risk and obesity may be proposed to begin at higher BMI levels, or there may be some other, stronger contributing factors.

Anaforoglu et al. [30] demonstrated that cases diagnosed according to the NIH criteria, usually referred to as the classical PCOS patients, have higher HOMA-IR and triglyceride levels than patients diagnosed with the Rotterdam 2003 criteria. Their findings again underline the impact of the amount of fat tissue on the PCOS phenotype as their NIH patients were heavier (30.3 ± 8.4 vs. 28.1 ± 6.4), even though this was statistically insignificant ($p = 0.065$). In our study group, we also compared the classical PCOS cases with the newly defined phenotypes of the Rotterdam 2003 criteria regarding CV risk profiles and demonstrated no difference. The similar risk profiles of our two groups may again be attributed to their indifferent mean BMI values, which were below the obesity threshold.

The limitations of the present study should be considered. First is the measurement of serum testosterone levels using a nonvalidated method. However, the gold standard method (LC-MS/MS) is not readily available in our country. A second limitation is that we did not measure waist circumference for determining central obesity. Instead the BMI calculations were performed in order to avoid taking the risk of possible millimetric measurement faults in our relatively normally weighted PCOS population.

Conclusion

The similar risk profiles at mean BMI levels below the obesity cutoff in this study provide a clue for the possible impact of adiposity. From a clinical standpoint, we believe that overweight and obese PCOS cases require more attention.

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References

1 Ruige JB, Assendelft WJ, Dekker JM, et al: Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 1998;97:996–1001.

2 Rutter MK, Meigs JB, Sullivan LM, et al: Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes 2005;54:3252–3257.

3 Boudreaux MY, Talbott EO, Kip KE, et al: Risk of T2DM and impaired fasting glucose among PCOS subjects: results of an 8-year follow-up. Curr Diab Rep 2006;6:77–83.

4 Ehrmann DA, Liljenquist DR, Kasza K, et al: Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:48–53.

5 Clayton RN, Ogden V, Hodgkinson J, et al: How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? Clin Endocrinol 1992;37:127–134.

6 Amato MC, Verghi M, Galluzzo A, et al: The oligomenorrhoic phenotypes of polycystic ovary syndrome are characterized by a high visceral adiposity index: a likely condition of cardiometabolic risk. Hum Reprod 2011;26:1486–1494.

7 Zawdaki J, Dunaif A: Diagnostic criteria for polycystic ovary syndrome: towards a rational approach; in Dunaif A, Givens J, Haseltine F, Marrian G (eds): Polycystic Ovary Syndrome. Current Issues in Endocrinology and Metabolism. Boston, Blackwell Scientific, 1992, vol 4, pp 377–384.

8 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 2004;81:19–25.

9 Welt CK, Gudmundsson JA, Arason G, et al: Characterizing discrete subsets of polycystic ovary syndrome as defined by the Rotterdam criteria: the impact of weight on phenotype and metabolic features. J Clin Endocrinol Metab 2006;91:4842–4848.

10 Carmina E, Chu MC, Longo RA, et al: Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. J Clin Endocrinol Metab 2005;90:2545–2549.

11 Carmina E, Rosato F, Jannì A, et al: Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006;91:2–6.
12 Johnstone EB, Rosen MP, Neril R, et al: The polycystic ovary post-Rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. J Clin Endocrinol Metab 2010;95:4965–4972.
13 Wang ET, Cirillo PM, Vittinghoff E, et al: Menstrual irregularity and cardiovascular mortality. J Clin Endocrinol Metab 2011;96:114–118.
14 Panidis D, Tziomalos K, Chatzis P, et al: Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome. Eur J Endocrinol 2013;168:145–152.
15 DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:214–223.
16 World Health Organization: Obesity: Preventing and Managing the Global Epidemic. Technical Report Series No. 894. Geneva, World Health Organization, 2000.
17 Ferriman D, Gallwey JD: Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961;21:1440–1447.
18 Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
19 Wild RA, Carmina E, Diamanti-Kandarakis E, et al: Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome. J Clin Endocrinol Metab 2010;95:2038–2049.
20 Legro RS, Arslanian SA, Ehrmann DA, et al: Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013;98:4565–4592.
21 Alphan Z, Berberoglu Z, Gorar S, et al: Increased total renin levels but not angiotensin-converting enzyme activity in obese patients with polycystic ovary syndrome. Med Princ Pract 2013;22:475–479.
22 Svendsen PF, Nilas L, Nørgaard K, et al: Obesity, body composition and metabolic disturbances in polycystic ovary syndrome. Hum Reprod 2008;23:2113–2121.
23 Moran LJ, Misso ML, Wild RA, et al: Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010;16:347–363.
24 Panidis D, Tziomalos K, Misichronis G, et al: Insulin resistance and endocrine characteristics of the different phenotypes of polycystic ovary syndrome: a prospective study. Hum Reprod 2012;27:541–549.
25 Barber TM, McCarthy MI, Wass JA, et al: Obesity and polycystic ovary syndrome. Clin Endocrinol 2006;65:137–145.
26 Ketel IJ, Stehouwer CD, Henry RM, et al: Greater arterial stiffness in polycystic ovary syndrome (PCOS) is an obesity- but not a PCOS-associated phenomenon. J Clin Endocrinol Metab 2010;95:4566–4575.
27 Rizzo M, Berneis K, Hersberger M, et al: Milder forms of atherogenic dyslipidemia in ovulatory versus anovulatory polycystic ovary syndrome phenotype. Hum Reprod 2009;24:2286–2292.
28 Jovanovic VP, Carmina E, Lobo RA: Not all women diagnosed with PCOS share the same cardiovascular risk profiles. Fertil Steril 2010;94:826–332.
29 Mehrabian F, Khani B, Kelishadi R, et al: The prevalence of metabolic syndrome and insulin resistance according to the phenotypic subgroups of polycystic ovary syndrome in a representative sample of Iranian females. J Res Med Sci 2011;16:763–769.
30 Anaforoglu I, Algun E, Incecayir O, et al: Higher metabolic risk with National Institutes of Health versus Rotterdam diagnostic criteria for polycystic ovarian syndrome in Turkish women. Metab Syndr Relat Disord 2011;9:375–380.