HORMONES 2015, 14(3):431-437

Research paper

Associations of menstrual cycle irregularities with age, obesity and phenotype in patients with polycystic ovary syndrome

Dimitrios Panidis,[1] Konstantinos Tziomalos,[2] Efstathios Papadakis,[1] Panagiotis Chatzis,[1] Eleni A. Kandaraki,[1] Elena A. Tsourdi,[1] Djuro Macut,[3] Jelica Bjekic-Macut,[4] Apostolos Marthopoulos,[1] Ilias Katsikis[1]

[1]Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Hippokration Hospital; [2]First Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, AHEPA Hospital; Thessaloniki, Greece; [3]Clinic for Endocrinology, Diabetes and Diseases of Metabolism; [4]CHC Bezanijska kosa; Faculty of Medicine, University of Belgrade, Belgrade, Serbia

ABSTRACT

OBJECTIVE: Limited data suggest that menstrual cycle abnormalities are more pronounced in younger and more obese patients with polycystic ovary syndrome (PCOS). We aimed to evaluate the association between menstrual cycle pattern and age, obesity and PCOS phenotype in a large population of women with PCOS. DESIGN: We studied 1,297 women with PCOS and divided them according to: a) age in ≤20, 21-30 and >30 years old, b) body mass index in normal weight, overweight and obese and c) PCOS phenotype in phenotype 1 (anovulation, hyperandrogenemia and polycystic ovaries), 2 (anovulation and hyperandrogenemia without polycystic ovaries), 3 (hyperandrogenemia and polycystic ovaries without anovulation) and 4 (anovulation and polycystic ovaries without hyperandrogenemia). RESULTS: The proportion of women with regular menstrual cycles progressively increased in the older age groups, being 8.1, 10.5 and 12.7% in women ≤20, 21-30 and >30 years old, respectively (p=0.037). The proportion of women with regular menstrual cycles did not differ between normal weight and obese women but was higher in overweight women (9.3, 9.4 and 13%, respectively; p=0.020). The proportion of women with regular cycles alternating with irregular cycles was highest in women with phenotype 4, intermediate in women with phenotype 2 and lowest in women with phenotype 1 (74.3, 69.4 and 61.7%, respectively; p=0.027). CONCLUSIONS: Menstrual cycle pattern is more irregular in women with the "classic" PCOS phenotypes than in phenotype 4 but appears to normalize with ageing. On the other hand, obesity does not appear to have an important effect on menstrual cycle pattern in PCOS.

Key words: Age, Androgens, Insulin resistance, Menstrual cycle, Obesity, Phenotype, Polycystic ovary syndrome

Address for correspondence:
Konstantinos Tziomalos, MD, PhD, First Propedeutic Department of Internal Medicine, AHEPA Hospital, 1 Stilponos Kyriakidi Str, 546 36 Thessaloniki, Greece, Tel. +30 2310994621, Fax + 30 2310274434, E-mail: ktziomalos@yahoo.com

Received: 28-07-2013, Accepted: 05-11-2013

INTRODUCTION

Polycystic ovary syndrome is the commonest endocrine disorder in women of reproductive age and the leading cause of anovulatory infertility.[1] However, PCOS is a heterogeneous disorder and not all women with PCOS are anovulatory.[1,2] Indeed, according to the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) definition of PCOS, at least two of the following three features should be present to establish the diagnosis of PCOS: a) oligo- or anovulation, b) biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia and c) polycystic ovaries on ultrasound, resulting in four different PCOS phenotypes.[2] Therefore, ovulatory women with hyperandrogenemia and polycystic ovaries (phenotype 3) are considered to suffer from PCOS.[2] However, it is unclear whether the severity of menstrual cycle irregularity, a surrogate marker of anovulation, differs between the three different anovulatory PCOS phenotypes.

Small retrospective studies reported a restoration of ovulation with ageing in women with PCOS.[3-5] However, none of these studies described in detail the menstrual cycle pattern in different age groups of PCOS patients.[3-5] In addition, women with PCOS are frequently obese[1] and obesity is associated with menstrual cycle abnormalities in the general population.[6-8] On the other hand, studies in women with PCOS yielded contradictory results regarding the relationship between obesity and menstrual cycle pattern.[4,9-12]

We aimed to assess in a large population of women with PCOS the association between menstrual cycle pattern and age, obesity and PCOS phenotype.

PATIENTS AND METHODS

Patients

We studied 1,297 women with PCOS [age 24.3±5.8 years, body mass index (BMI)]. Diagnosis of PCOS was based on the revised Rotterdam criteria, which require the presence of at least two of the following three features: a) oligo- or anovulation (<8 spontaneous hemorrhagic episodes/yr), b) biochemical hyperandrogenemia (defined in our population as early follicular phase testosterone >60 ng/dl, corresponding to the mean+2 SD testosterone levels in 200 control subjects measured in our laboratory) or clinical manifestations of hyperandrogenemia (Ferriman-Gallwey score ≥8) and c) polycystic ovaries on ultrasound (≥12 small follicles in at least one ovary and/or ovarian volume >10cm^3).[2]

None of the women studied had galactorrhea or any endocrine or systemic disease that could possibly affect reproductive physiology. No woman reported use during the last semester of any medication that could interfere with the normal function of the hypothalamic-pituitary-gonadal axis. When basic 17α-hydroxyprogesterone (17α-OHP) levels were >1.5 ng/ml, the Synacthen test (0.25 mg/1ml; Novartis Pharma S.A., Rueil-Malmaison, France) was performed to rule out congenital adrenal hyperplasia. Other causes of hyperandrogenemia, including prolactinoma, Cushing's syndrome and androgen secreting tumors were also excluded.

Study protocol

In all women, weight, height, waist circumference (W) and hip circumference (H) were measured. Body weight was measured with an analog scale and in light clothing; height was measured barefoot with a stadiometer. The BMI was calculated by dividing weight (in kg) by height squared (in m) to assess obesity. The W was obtained as the smallest circumference at the level of the umbilicus and the H was measured at the level of the widest diameter around the buttocks. The W to H ratio (W/H) was calculated by dividing W by H.

Baseline blood samples were collected between days 3 and 7 of the menstrual cycle in women with regular menstrual cycles and after a spontaneous bleeding episode in women with menstrual cycle abnormalities, after an overnight fast. The circulating levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), total testosterone (T), Δ_4-androstenedione (Δ_4-A), dehydroepiandrosterone sulfate (DHEA-S), 17α-OHP, sex hormone-binding globulin (SHBG), glucose and insulin were measured. Immediately after baseline blood sampling, an oral glucose tolerance test (OGTT) was performed; 75 g of glucose were administered orally and serum glucose levels were determined after 30, 60, 90 and 120

min. On the same day, transvaginal ultrasonography was performed and the volume of each ovary was determined as well as the number of small follicles (measuring 2-9 mm in diameter) in each ovary.

The study population was divided according to: a) age ≤20 years old (n=381), 21-30 years old (n=717) and >30 years old (n=199), b) BMI in normal weight (i.e. with BMI <25 kg/m^2; n=679), overweight (i.e. with BMI 25-29.9 kg/m^2; n=277) and obese (i.e. with BMI ≥30 kg/m^2; n=341), c) W in women with and without abdominal obesity [i.e. with W ≥ or <80 cm (n=652 and n=645, respectively) or with W ≥ or <88 cm (n=431 and n=866, respectively)] and d) PCOS phenotype in women with phenotype 1 (i.e. with oligo- or anovulation, hyperandrogenism and polycystic ovaries; n=653), phenotype 2 (i.e. with oligo- or anovulation and hyperandrogenism but without polycystic ovaries; n=408), phenotype 3 (i.e. with hyperandrogenism and polycystic ovaries but without oligo- or anovulation; n=131) and phenotype 4 (i.e. with oligo- or anovulation and polycystic ovaries but without hyperandrogenism; n=105).[2]

The pattern of menstrual cycles was divided as described previously[13] into: a) single cycle irregularities (primary amenorrhea, secondary amenorrhea, oligomenorrhea, polymenorrhea; n=148), b) multiple cycle irregularities (secondary amenorrhea alternating with oligomenorrhea, secondary amenorrhea alternating with polymenorrhea, oligomenorrhea alternating with polymenorrhea; n=254), c) regular menstrual cycles alternating with a single cycle irregularity (secondary amenorrhea, oligomenorrhea or polymenorrhea; n=764) and d) regular menstrual cycles (n=131). Primary amenorrhea was defined as absence of menstruation by the age of 16 years. Secondary amenorrhea was defined as absence of vaginal bleeding for at least six months after a period of established menstruation. Oligomenorrhea was defined as cycle length >35 days or <8 cycles/year. Polymenorrhea was defined as cycle length ≤21 days. Regular menstrual cycles were defined as cycle length 28±4 days.

Methods

Serum FSH, LH, PRL, androgen, 17α-OHP, SHBG, glucose and insulin levels were measured as previously described.[14] Free androgen index (FAI) was determined as follows: FAI = T (nmol/l) x 100 / SHBG (nmol/l).[15] The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as follows: HOMA-IR = fasting insulin (μIU/ml) x fasting glucose (mg/dl) / 405.[16] The quantitative insulin sensitivity check index (QUICKI) was calculated according to the following formula: QUICKI = 1 / [logInsulin (μIU/ml) + logGlucose (mg/dl)].[17]

Transvaginal ultrasonography

Transvaginal ultrasound scans of the ovaries were performed in all women by an experienced sonographer. Ovarian volume was calculated by the formula: $V = (\pi/6) \times D_{length}$ x $D_{width} \times D_{thickness}$, where D is dimension. The presence of polycystic ovaries was diagnosed by the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 cm^3).

Statistical analysis

Data analysis was performed with the statistical package SPSS (version 17.0; SPSS Inc., Chicago, IL). Data are reported as mean±SD. Differences in the prevalence of the different patterns of menstrual cycles between age and BMI groups and between PCOS phenotypes were assessed with the chi-square test. Differences in anthropometric characteristics between women with different patterns of menstrual cycles were assessed with one-way analysis of variance via the Holm-Sidak method for multiple comparison testing. In all cases, a p value <0.05 was considered significant.

RESULTS

The age of women with different patterns of menstrual cycles is shown in Table 1. Women with either single or multiple cycle irregularities and no regular cycles were younger than women with regular cycles (23.2±6.6, 23.7±5.5 and 25.7±5.7 years-old, respectively; p=0.001 and p=0.007, respectively). The prevalence of the different patterns of menstrual cycle in the different age groups is shown in Table 2. The proportion of women who had regular menstrual cycles progressively increased in the older age groups, being 8.1, 10.5 and 12.7% in women ≤20, 21-30 and >30 years-old, respectively (p=0.037). In addition, among women with irregular menstrual cycles, the proportion of women who had "milder" cycle abnor-

Table 1. Age and anthropometric characteristics of women with polycystic ovary syndrome and different patterns of menstrual cycles

	Single cycle irregularity (n=148)	Multiple cycle irregularities (n=254)	Single cycle irregularity alternating with regular menstrual cycles (n=764)	Regular menstrual cycles (n=131)	p (overall)	p (Post-hoc tests between women with different types of menstrual cycle irregularities) SCI vs. MCI	SCI vs. SCI/ RMC	SCI vs. RMC	MCI vs. SCI/ RMC	MCI vs. RMC	SCI/ RMC vs. RMC
Age (years)	23.2±6.6	23.7±5.5	24.4±5.7	25.7±5.7	0.001	NS	NS	0.001	NS	0.007	NS
BMI (kg/m^2)	27.9±8.2	26.2±7.2	26.7±6.9	26.6±5.6	NS	NA	NA	NA	NA	NA	NA
Waist (cm)	86.3±17.8	82.8±16.1	83.7±15.3	82.0±11.8	NS	NA	NA	NA	NA	NA	NA
W/H	0.84±0.54	0.78±0.07	0.78±0.07	0.77±0.06	0.013	0.033	0.016	0.033	NS	NS	NS

SCI: single cycle irregularity; MCI: multiple cycle irregularities; SCI/RMC: single cycle irregularity alternating with regular menstrual cycles; RMC: regular menstrual cycles; NS: not significant; NA: not applicable; BMI: body mass index; W/H: waist/hip ratio.

Table 2. Prevalence of the different patterns of menstrual cycles in the different age groups of women with polycystic ovary syndrome (p = 0.037)

	≤20 years old (n = 381)	21-30 years old (n = 717)	>30 years old (n = 199)
Single cycle irregularity	15.0	9.5	11.6
Multiple cycle irregularities	21.3	19.9	14.6
Single cycle irregularity alternating with regular menstrual cycles	55.6	60.1	61.1
Regular menstrual cycles	8.1	10.5	12.7

malities (i.e. regular cycles alternating with a cycle irregularity) also increased with ageing, whereas the proportion of women who had more "severe" cycle abnormalities (i.e. either single or multiple cycle irregularities and no regular cycles) declined (Table 2).

The anthropometric characteristics of women with different patterns of menstrual cycles are shown in Table 1. The BMI and W did not differ between groups. The prevalence of the different patterns of menstrual cycles in the different BMI groups is shown in Table 3. The proportion of women with regular menstrual cycles did not differ between normal weight and obese women but was higher in overweight women (9.3, 9.4 and 13%, respectively; p = 0.020). Moreover, among women with irregular menstrual cycles, the proportion of women with regular cycles alternating with a cycle irregularity did not differ between normal weight and obese women but was higher in overweight women (58.3, 56.5 and 63.5%, respectively; p = 0.020). The prevalence of the different patterns of menstrual cycles did not differ between women with abdominal obesity and those without abdominal obesity, regardless of the cut-off value of W used for defining abdominal obesity (i.e. ≥80 cm or ≥88 cm; Table 4).

All women with phenotype 3 had regular cycles and were thus excluded from the analysis of the as-

Table 3. Prevalence of the different patterns of menstrual cycles in the different body mass index (BMI) groups of women with polycystic ovary syndrome (p = 0.020)

	Normal weight (n = 679)	Overweight (n = 277)	Obese (n = 341)
Single cycle irregularity	10.8	8.7	15.0
Multiple cycle irregularities	21.6	14.8	19.1
Single cycle irregularity alternating with regular menstrual cycles	58.3	63.5	56.5
Regular menstrual cycles	9.3	13.0	9.4

Normal weight: women with BMI <25.0 kg/m^2; overweight: women with BMI 25.0-25.9 kg/m^2; obese: women with BMI ≥30 kg/m^2.

sociation between PCOS phenotype and the pattern of menstrual cycle. The anthropometric characteristics of women with phenotypes 1, 2 and 4 are shown in Table 5. Women with phenotype 1 were younger than both women with phenotype 2 and women with phenotype 4 (23.5±5.3, 24.6±6.2 and 26.1±6.4 years-old, respectively; p=0.008 and p <0.001, respectively), whereas the latter two phenotypes did not differ in age. On the other hand, women with phenotype 1 and women with phenotype 2 had comparable BMI (26.9±7 and 27.2±7.4 kg/m^2, respectively) and both had higher BMI than women with phenotype 4 (24.5±6.1 kg/m^2; p = 0.004 and p = 0.002 compared with women with phenotype 1 and 2, respectively). The prevalence of the different patterns of menstrual cycles in phenotypes 1, 2 and 4 is shown in Table 6. None of the women with these phenotypes had persistently regular cycles. However, the proportion of women with regular cycles alternating with irregular cycles was highest in women with phenotype 4, intermediate in women with phenotype 2 and lowest in women with phenotype 1 (74.3, 69.4 and 61.7%, respectively; p = 0.027).

Table 4. Prevalence of the different patterns of menstrual cycles in women with polycystic ovary syndrome with and without abdominal obesity, defined as waist circumference (W) ≥80 cm or ≥88 cm (p = NS for both cut-off values)

	Women with W ≥80 cm (n = 652)	Women with W <80 cm (n = 645)	Women with W ≥88 cm (n = 431)	Women with W <88 cm (n = 866)
Single cycle irregularity	11.9	11.2	14.6	10.0
Multiple cycle irregularities	17.6	22.0	18.6	20.5
Single cycle irregularity alternating with regular menstrual cycles	60.5	55.6	57.1	58.4
Regular menstrual cycles	10.0	11.2	9.7	11.1

Table 5. Anthropometric characteristics in women with phenotypes 1, 2 and 4 of the polycystic ovary syndrome

	Phenotype 1 (n = 653)	Phenotype 2 (n = 408)	Phenotype 4 (n = 105)	p (overall)	p (Post-hoc tests between phenotypes)		
					1 vs. 2	1 vs. 4	2 vs. 4
Age (years)	23.5±5.3	24.6±6.2	26.1±6.4	<0.001	0.008	<0.001	NS
BMI (kg/m^2)	26.9±7.0	27.2±7.4	24.5±6.1	0.002	NS	0.004	0.002
Waist (cm)	84.7±16.2	84.0±15.6	78.3±12.8	0.001	NS	<0.001	0.003
W/H	0.79±0.07	0.78±0.07	0.82±0.61	NS	NA	NA	NA

NS: not significant; NA: not applicable; BMI: body mass index; W/H: waist/hip ratio.
Phenotype 1: women with oligo- or anovulation, hyperandrogenemia and polycystic ovaries; phenotype 2: women with oligo- or anovulation and hyperandrogenemia but without polycystic ovaries; phenotype 4: women with oligo- or anovulation and polycystic ovaries but without hyperandrogenemia.

Table 6. Prevalence of the different patterns of menstrual cycles in women with phenotypes 1, 2 and 4 of the polycystic ovary syndrome (p = 0.027)

	Phenotype 1 (n = 653)	Phenotype 2 (n = 408)	Phenotype 4 (n = 105)
Single cycle irregularity	14.1	11.7	7.6
Multiple cycle irregularities	24.2	18.9	18.1
Single cycle irregularity alternating with regular menstrual cycles	61.7	69.4	74.3
Regular menstrual cycles	0.0	0.0	0.0

Phenotype 1: women with oligo- or anovulation, hyperandrogenemia and polycystic ovaries; phenotype 2: women with oligo- or anovulation and hyperandrogenemia but without polycystic ovaries; phenotype 4: women with oligo- or anovulation and polycystic ovaries but without hyperandrogenemia.

DISCUSSION

We report a normalization of menstrual cycles with ageing in patients with PCOS. Indeed, the proportion of patients with regular cycles – either alone or in combination with irregular cycles – increased in older subjects, whereas the proportion of patients without any regular cycles declined. Previous retrospective studies reported spontaneous restitution of cyclic regularity with ageing in women with PCOS but were considerably smaller (n = 33, 205 and 254, respectively), evaluated women of a shorter age range (>40 years, >30 years and 25-31 years, respectively) and did not report in detail the menstrual cycle pattern.[3-5] Other small studies (n = 118 and 204, respectively) focused only on patients with PCOS and a single cycle irregularity and also reported that patients with regular menstrual cycles were older than patients with either amenorrhea or oligomenorrhea.[11,12] It is possible that the progressive decline in circulating androgens or follicle loss with age in patients with PCOS contributes to this progressive improvement in menstrual cycle abnormalities.[5,18-20]

Studies in the general population showed that obesity is associated with irregular menstrual cycles.[6-8] Interestingly, the proportion of women with regular menstrual cycles did not differ between normal weight and obese women or between women with and without abdominal obesity in our study. On the other hand, overweight women more frequently presented with regular menstrual cycles. Previous smaller studies in patients with PCOS reported discrepant results regarding the relationship between obesity and menstrual cycle abnormalities. Some investigators reported higher rates of menstrual disorders in overweight/obese patients,[9,10,12] others did not identify differences in BMI between women with amenorrhea, oligomenorrhea and regular menstrual cycles[11] and in other reports women with regular cycles were more obese than those with irregular cycles.[4] On the other hand, diet-induced weight loss in patients with PCOS results in resumption of ovulation,[21-23] while hyperandrogenemia and IR, both of which contribute to anovulation, are more severe in overweight/obese patients with PCOS.[9,24-26] Therefore, obesity appears to have an adverse effect on reproductive function in patients with PCOS, but this effect might be less pronounced than in the general population, possibly because of the overwhelming effects of hyperandrogenemia.

The proportion of women with milder cycle abnormalities (i.e. with some regular cycles alternating with irregular cycles) was highest in women with phenotype 4, intermediate in women with phenotype 2 and lowest in women with phenotype 1. We are not aware of any previous studies that compared menstrual cycle patterns between the anovulatory phenotypes of PCOS. Women with phenotype 1 were younger than women with phenotypes 2 and 3 and this might have contributed to the more irregular cycle pattern in phenotype 1. In addition, women with phenotype 1 have higher serum androgen levels and more severe IR than women with phenotype 2[27-29] and both these phenotypes have by definition more pronounced hyperandrogenemia than women with phenotype 4. Finally, the higher BMI in women with phenotypes 1 and 2 than in women with phenotype 4 might also have played a role in the higher prevalence of abnormal cycles in the former phenotypes.

In conclusion, menstrual cycle pattern is more irregular in women with the "classic" PCOS phenotypes than in phenotype 4 but appears to normalize with ageing. On the other hand, obesity does not appear to have an important effect on menstrual cycle pattern in PCOS. Given the association between irregular menstrual cycles and increased risk for both type 2 diabetes mellitus and cardiovascular events,[30-32] cardiovascular prevention measures should primarily focus on women with the classic PCOS phenotypes and on ageing women with persistently irregular cycles.

REFERENCES

1. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R, 2011 Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 7: 219-231.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19: 41-47.
3. Dahlgren E, Johansson S, Lindstedt G, et al, 1992 Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril 57: 505-513.
4. Elting MW, Korsen TJ, Rekers-Mombarg LT, Schoemaker J, 2000 Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. Hum Reprod 15: 24-28.
5. Brown ZA, Louwers YV, Fong SL, et al, 2011 The

phenotype of polycystic ovary syndrome ameliorates with aging. Fertil Steril 96: 1259-1265.
6. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA, 1979 The association of obesity with infertility and related menstural abnormalities in women. Int J Obes 3: 57-73.
7. Hartz AJ, Rupley DC, Rimm AA, 1984 The association of girth measurements with disease in 32,856 women. Am J Epidemiol 119: 71-80.
8. Rowland AS, Baird DD, Long S, et al, 2002 Influence of medical conditions and lifestyle factors on the menstrual cycle. Epidemiology 13: 668-674.
9. Kiddy DS, Sharp PS, White DM, et al, 1990 Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. Clin Endocrinol (Oxf) 32: 213-220.
10. Balen AH, Conway GS, Kaltsas G, et al, 1995 Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod 10: 2107-2111.
11. Cupisti S, Kajaia N, Dittrich R, Duezenli H, Beckmann MW, Mueller A, 2008 Body mass index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. Eur J Endocrinol 158: 711-719.
12. Strowitzki T, Capp E, von Eye Corleta H, 2010 The degree of cycle irregularity correlates with the grade of endocrine and metabolic disorders in PCOS patients. Eur J Obstet Gynecol Reprod Biol 149: 178-181.
13. Panidis D, Tziomalos K, Chatzis P, et al, 2013 Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome. Eur J Endocrinol 168: 145-152.
14. Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D, 2009 Anti-Müllerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 296: E238-243.
15. Carter GD, Holland SM, Alaghband-Zadeh J, Rayman G, Dorrington-Ward P, Wise PH, 1983 Investigation of hirsutism: testosterone is not enough. Ann Clin Biochem 20: 262-263.
16. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R, 1985 Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 12-19.
17. Katz A, Nambi SS, Mather K, et al, 2000 Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85: 2402-2410.
18. Kumar A, Woods KS, Bartolucci AA, Azziz R, 2005 Prevalence of adrenal androgen excess in patients with the polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf) 62: 644-649.
19. Carmina E, Campagna AM, Lobo RA, 2012 A 20-year follow-up of young women with polycystic ovary syndrome. Obstet Gynecol 119: 263-269.
20. Panidis D, Tziomalos K, Macut D, et al, 2012 Cross-sectional analysis of the effects of age on the hormonal, metabolic, and ultrasonographic features and the prevalence of the different phenotypes of polycystic ovary syndrome. Fertil Steril 97: 494-500.
21. Kiddy DS, Hamilton-Fairley D, Bush A, et al, 1992 Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 36: 105-111.
22. Huber-Buchholz MM, Carey DG, Norman RJ, 1999 Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 84: 1470-1474.
23. Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G, 2003 Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 18: 1928-1932.
24. Holte J, Bergh T, Gennarelli G, Wide L, 1994 The independent effects of polycystic ovary syndrome and obesity on serum concentrations of gonadotrophins and sex steroids in premenopausal women. Clin Endocrinol (Oxf) 41: 473-481.
25. Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Baumann G, Yen SS, 1996 Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metab 81: 2854-2864.
26. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Tapanainen JS, 2000 Insulin sensitivity, insulin secretion, and metabolic and hormonal parameters in healthy women and women with polycystic ovarian syndrome. Hum Reprod 15: 1266-1274.
27. Loucks TL, Talbott EO, McHugh KP, Keelan M, Berga SL, Guzick DS, 2000 Do polycystic-appearing ovaries affect the risk of cardiovascular disease among women with polycystic ovary syndrome? Fertil Steril 74: 547-552.
28. Hahn S, Bering van Halteren W, Roesler S, et al, 2006 The combination of increased ovarian volume and follicle number is associated with more severe hyperandrogenism in German women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 114: 175-181.
29. Panidis D, Tziomalos K, Misichronis G, et al, 2012 Insulin resistance and endocrine characteristics of the different phenotypes of polycystic ovary syndrome: a prospective study. Hum Reprod 27: 541-549.
30. Solomon CG, Hu FB, Dunaif A, et al, 2001 Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. JAMA 286: 2421-2426.
31. Solomon CG, Hu FB, Dunaif A, et al, 2002 Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab 87: 2013-2017.
32. Dilbaz B, Ozkaya E, Cinar M, Cakir E, Dilbaz S, 2011 Cardiovascular disease risk characteristics of the main polycystic ovary syndrome phenotypes. Endocrine 39: 272-277.