CLINICAL STUDY

Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome

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Abstract

Objective: Insulin resistance (IR) is frequent in polycystic ovary syndrome (PCOS) and contributes to the increased risk for type 2 diabetes mellitus and cardiovascular disease of this population. Several markers of IR are used but most are expensive or have limited sensitivity and specificity. Preliminary data suggest that the menstrual cycle pattern correlates with IR in PCOS but existing studies are small. We aimed to assess the relationship between the type of menstrual cycle irregularities and IR in PCOS.

Design: Prospective study.

Methods: We studied 1285 women with PCOS, divided according to the menstrual cycle pattern.

Results: Patients with isolated secondary amenorrhea and those with secondary amenorrhea alternating with regular menstrual cycles were more insulin resistant than patients with regular cycles (Group D). Patients with isolated oligomenorrhea were also more insulin resistant than Group D. However, patients with oligomenorrhea alternating with regular cycles, secondary amenorrhea, or polymenorrhea had comparable levels of markers of IR with Group D. Moreover, patients with oligomenorrhea alternating with regular cycles were less insulin resistant than patients with secondary amenorrhea alternating with regular cycles. Finally, patients with isolated polymenorrhea and those with polymenorrhea alternating with regular cycles had comparable levels of markers of IR with Group D.

Conclusions: Amenorrhea is associated with more pronounced IR in PCOS, and oligomenorrhea portends a less excessive risk for IR than amenorrhea whereas polymenorrhea appears to be even more benign metabolically. Therefore, the type of menstrual cycle abnormality appears to represent a useful tool for identifying a more adverse metabolic profile in PCOS.

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Introduction

The polycystic ovary syndrome (PCOS) is a frequent endocrine disorder with considerable heterogeneity in its manifestations (1, 2). A substantial proportion of patients with PCOS have insulin resistance (IR), which results in increased risk for impaired glucose tolerance and type 2 diabetes mellitus (T2DM) (1, 2, 3, 4). Accumulating data suggest a higher incidence of cardiovascular disease (CVD) in this syndrome and IR appears to contribute to this increased risk (5, 6).

Given the frequent presence of IR in patients with PCOS and its association with adverse consequences (T2DM and CVD), it is important to identify patients with PCOS who are insulin resistant. Obesity is a major risk factor for IR both in the general population and in patients with PCOS (2, 7). However, IR can be present even in normal weight

patients with PCOS (8). Oligo- and anovulation are pivotal characteristics of PCOS and also appear to correlate with the presence of IR (1, 2). However, assessment of ovulation requires laboratory investigations and is costly. On the other hand, menstrual cycle irregularity is a relatively accurate surrogate of ovulation and is easily obtained from the medical history (1, 9). Therefore, menstrual cycle pattern might serve as a marker of IR in patients with PCOS, as IR can induce oligo- or anovulation and thus menstrual cycle irregularity by exacerbating hyperandrogenemia and by disrupting follicular growth (2). Nevertheless, very few small studies evaluated the association between menstruation abnormalities and the endocrine and metabolic characteristics in PCOS (10, 11, 12, 13).

We aimed to assess the relationship between menstrual cycle irregularities and both IR and circulating androgens

in a large cohort of patients with PCOS. We also aimed to determine whether different types of menstruation abnormalities are associated with more pronounced IR and hyperandrogenemia in this population.

Materials and methods

Patients

We studied 1285 women with PCOS (mean age 24.3 ± 5.8 years, mean BMI 26.7 ± 6.9 kg/m²) who were outpatients at the Gynecological Endocrinology Infirmary of the Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki. Diagnosis of PCOS was based on the revised criteria of Rotterdam (14). None of the women studied had galactorrhea or any endocrine or systemic disease that could possibly affect reproductive physiology. A Synacthen test was performed with tetracosactide (Synacthen 0.25 mg/1 ml; Novartis Pharma) in women with a basal 17α -hydroxyprogesterone (17α -OHP) plasma level > 1.5 ng/ml to exclude congenital adrenal hyperplasia. No woman reported use of any medication that could interfere with the normal function of the hypothalamic–pituitary–gonadal axis during the last semester.

Informed consent was obtained from all women, and the study was approved by the Institutional Review Board; the study met the requirements of the 1975 Helsinki guidelines.

Study protocol

In all women, weight, height, waist circumference (W), and hip circumference (H) were measured. Body weight was measured in light clothing using an analog scale and height was measured barefoot using a stadiometer. BMI was calculated by dividing weight (kilogram) by height squared (meter) 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 (WHR) 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 FSH, LH, prolactin (PRL), total testosterone, Δ_4 -androstenedione, DHEAS, 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 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.

Women with PCOS were divided according to the menstrual cycle pattern into i) women with a single cycle irregularity (i.e. with primary amenorrhea ($n=4$), secondary amenorrhea ($n=37$), oligomenorrhea ($n=95$), or polymenorrhea ($n=9$); Group A); ii) women with multiple cycle irregularities (i.e. with secondary amenorrhea alternating with oligomenorrhea ($n=82$) or polymenorrhea ($n=23$) and women with oligomenorrhea alternating with polymenorrhea ($n=147$); Group B); iii) women with regular menstrual cycles alternating with a single cycle irregularity (i.e. with secondary amenorrhea ($n=106$), oligomenorrhea ($n=598$), or polymenorrhea ($n=53$); Group C); and iv) women with regular menstrual cycles ($n=131$; Group D) (Fig. 1). Menstrual cycle data were obtained from a diary that women were keeping for 1 year before enrollment to the study. For the previous years, menstrual cycle data were provided from women from memory. Primary amenorrhea was defined as the absence of menstruation by the age of 16 years. Secondary amenorrhea was defined as absence of vaginal bleeding for at least 6 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 (15).

Methods

Serum FSH, LH, PRL, androgen, 17α -OHP, SHBG, glucose, insulin, TSH, and free thyroxine (FT₄) were measured as described previously (16). Free androgen index (FAI) was determined as follows: FAI = testosterone

Figure 1 Distribution of menstrual cycle pattern in the study population. PA, primary amenorrhea; SA, secondary amenorrhea; OM, oligomenorrhea; PM, polymenorrhea; SA/OM, secondary amenorrhea alternating with oligomenorrhea; SA/PM, secondary amenorrhea alternating with polymenorrhea; OM/PM, oligomenorrhea alternating with polymenorrhea; RC, regular cycles; RC/SA, regular cycles alternating with secondary amenorrhea; RC/OM, regular cycles alternating with oligomenorrhea; RC/PM, regular cycles alternating with polymenorrhea.

(nmol/l) $\times$ 100/SHBG (nmol/l) (17). The homeostasis model assessment of IR (HOMA-IR) index was calculated as follows: $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting glucose (mg/dl)} / 405$ (18). The quantitative insulin sensitivity check index (QUICKI) was calculated according to the following formula: $\text{QUICKI} = 1 / (\log \text{Insulin } (\mu\text{IU/ml}) + \log \text{Glucose (mg/dl)})$ (19).

Transvaginal ultrasonography

Transvaginal ultrasound scans of the ovaries were performed by an experienced sonographer in women who participated in the study. Ovarian volume was calculated by the formula: $V = (\pi/6) \times D_{\text{length}} \times D_{\text{width}} \times D_{\text{thickness}}$, 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 ($> 10 \text{ cm}^3$).

Statistical analysis

Data analysis was performed with the statistical package SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA). Data are reported as mean $\pm$ s.d. Differences between groups were assessed using one-way ANOVA with the Holm–Sidak method for multiple comparison testing. Correction for age, BMI, and W was carried out using analysis of covariance in comparisons among groups with differences in these parameters. Multiple regression analysis was performed to identify independent predictors of IR (assessed with the HOMA-IR) including in the analysis the BMI, the WHR, the menstrual pattern and circulating androgens (assessed with the FAI). In all cases, a P value < 0.05 was considered significant.

Results

Characteristics of women with primary amenorrhea are shown in Table 1. These women ($n=4$) did not differ in circulating androgens from Group D ($n=131$) except for FAI, which was higher in women with primary amenorrhea ($P=0.026$). In addition, women with primary amenorrhea were more insulin resistant than Group D.

Characteristics of women with isolated secondary amenorrhea ($n=37$) are shown in Table 1. These women did not differ in circulating androgens from Group D except for FAI and serum DHEAS levels, which were higher in women with isolated secondary amenorrhea ($P<0.001$ and $P=0.006$ respectively). In addition, women with isolated secondary amenorrhea were more insulin resistant than Group D. Characteristics of women with secondary amenorrhea alternating with regular menstrual cycles ($n=106$) are shown in Table 2. These women had higher circulating androgens and were more insulin resistant than Group D.

Characteristics of women with isolated oligomenorrhea ($n=95$) are shown in Table 1. These women did not differ in circulating androgens from Group D except for FAI, which was higher in women with isolated oligomenorrhea ($P=0.009$). In addition, women with isolated oligomenorrhea were more insulin resistant than Group D. In contrast, women with oligomenorrhea alternating with regular menstrual cycles, secondary amenorrhea, or polymenorrhea had comparable levels of circulating androgens and markers of IR with Group D (Tables 2 and 3). On the other hand, women with oligomenorrhea alternating with regular menstrual cycles had lower circulating androgens and were less insulin resistant than women with secondary amenorrhea alternating with regular menstrual cycles (Table 2).

Characteristics of women with isolated polymenorrhea ($n=9$) are shown in Table 1. These women did not differ in circulating androgens or markers of IR from Group D. Similarly, women with polymenorrhea alternating with regular menstrual cycles had comparable levels of circulating androgens and markers of IR with Group D (Table 2). In contrast, women with polymenorrhea alternating with regular menstrual cycles had lower circulating androgens than women with secondary amenorrhea alternating with regular menstrual cycles. In addition, women with polymenorrhea alternating with regular menstrual cycles were less insulin resistant than women with regular menstrual cycles alternating with either secondary amenorrhea or oligomenorrhea. Finally, women with polymenorrhea alternating with oligomenorrhea had lower FAI than women with secondary amenorrhea alternating with either polymenorrhea or oligomenorrhea ($P=0.003$ and $P=0.006$ respectively) whereas markers of IR were comparable (Table 3).

In multiple regression analysis, independent predictors of HOMA-IR were the BMI ($P<0.001$), the FAI ($P=0.028$), and the menstrual pattern ($P<0.001$). In *post hoc* analysis, among the different types of menstrual pattern, only primary amenorrhea, isolated secondary amenorrhea, isolated oligomenorrhea, and secondary amenorrhea alternating with oligomenorrhea were independent predictors of HOMA-IR compared with Group D ($P<0.001$, $P=0.004$, $P=0.004$, and $P=0.037$ respectively).

Discussion

This is the largest study that evaluated the association between menstrual cycle pattern and IR/androgen levels in patients with PCOS. We report that patients with isolated primary amenorrhea, secondary amenorrhea, or oligomenorrhea and patients with secondary amenorrhea alternating with regular menstrual cycles had more pronounced IR than Group D. In contrast, patients with oligomenorrhea alternating with

Table 1 Characteristics of women with PCOS and a single cycle irregularity and of women with PCOS and regular menstrual cycles (RMC).

	PA	SA	OM	PM	RMC	P (overall)	P**							
							PA vs SA	PA vs OM	PA vs PM	SA vs OM	SA vs PM	OM vs PM		
n	4	37	95	9	131									
Age (years)	17.4±0.7	22.0±6.4 [§]	23.7±6.5	22.6±7.8	25.7±5.7	0.001	NS	NS	NS	NS	NS	NS	NS	NS
BMI (kg/m ²)	26.4±9.4	28.1±7.3	27.7±8.3	28.7±10.1	26.6±5.6	NS	NA	NA	NA	NA	NA	NA	NA	NA
W (cm)	83.4±31.9	86.9±16.4	85.3±17.7	91.6±19.1	82.0±11.8	NS	NA	NA	NA	NA	NA	NA	NA	NA
W/H	0.79±0.16	0.97±1.04	0.79±0.07	0.81±0.07	0.77±0.06	NS	NA	NA	NA	NA	NA	NA	NA	NA
FSH (IU/l)	9.1±5.2*	5.6±1.9	5.5±1.5 [†]	5.6±1.2	6.2±1.7	<0.001	0.002	0.001	0.013	NS	NS	NS	NS	NS
LH (IU/l)	22.9±25.9*	8.8±5.7 [§]	7.6±5.6	10.3±6.9 [§]	6.1±3.9	<0.001	<0.001	<0.001	0.002	NS	NS	NS	NS	NS
Prolactin (ng/ml)	11.8±9.9	12.1±5.8 [†]	12.7±5.9 [†]	17.1±11.4	14.7±6.9	0.006	NS	NS	NS	NS	NS	NS	NS	NS
Testosterone (nmol/l)	77.5±37.9	83.6±30.8	79.5±34.1	72.9±20.7	73.6±27.3	NS	NA	NA	NA	NA	NA	NA	NA	NA
Δ ₄ -A (nmol/l)	2.4±0.4	2.7±0.7	2.9±1.3	2.9±1.4	2.8±1.1	NS	NA	NA	NA	NA	NA	NA	NA	NA
DHEAS (μg/l)	2795.4±631.2	2554.1±986.1 [†]	2901.3±1343.9	2480.2±1272.6	3158.3±1319.9	0.047	NS	NS	NS	NS	NS	NS	NS	NS
FAI	16.58±9.53 [§]	13.66±9.69*	10.26±8.9 [†]	8.93±3.85	7.52±4.37	<0.001	NS	NS	NS	NS	NS	NS	NS	NS
17α-OHP (nmol/l)	1.1±0.1	1.1±0.4	1.1±0.5	1.2±0.5	1.1±0.6	NS	NA	NA	NA	NA	NA	NA	NA	NA
SHBG (nmol/l)	18.9±8.2	30.5±19.8	42.0±37.5	34.9±19.2	42.7±23.6	NS	NA	NA	NA	NA	NA	NA	NA	NA
Glucose (mmol/l)	86.2±18.64	97.5±14.2	97.9±29.2	106.2±17.3	96.5±11.5	NS	NA	NA	NA	NA	NA	NA	NA	NA
Insulin (pmol/l)	54.3±70.54*	17.7±17.3 [†]	14.2±8.9 [§]	20.2±18.3	10.4±6.4	<0.001	<0.001	<0.001	<0.001	NS	NS	NS	NS	NS
Glucose/insulin	3.54±2.09 [§]	9.30±6.35 [§]	9.62±6.52 [†]	7.32±3.15	12.57±7.65	0.002	NS	NS	NS	NS	NS	NS	NS	NS
AUC OGTT	17 100.0±2869.9	16 415.3±4290.3	15 266.3±2891.9	16 893.7±4168.3	15 029.4±2577.6	NS	NA	NA	NA	NA	NA	NA	NA	NA
HOMA-IR	11.55±14.75*	4.49±5.04 [§]	3.77±4.79 [§]	5.90±6.61	2.52±1.64	<0.001	0.010	0.002	NS	NS	NS	NS	NS	NS
QUICKI	0.29±0.04 [†]	0.33±0.03 [†]	0.33±0.03 [†]	0.31±0.03	0.34±0.03	<0.001	NA	NA	NA	NA	NA	NA	NA	NA
Ovarian volume (cm ³)	5.9±3.5	9.6±5.1	8.5±4.6	7.7±7.8	8.1±3.4	NS	NA	NA	NA	NA	NA	NA	NA	NA
Ovarian follicles	7.2±3.8	14.3±7.7	12.7±7.5	11.7±6.6	11.8±3.9	NS	NA	NA	NA	NA	NA	NA	NA	NA

PA, primary amenorrhea; OM, oligomenorrhea; SA, secondary amenorrhea; PM, polymenorrhea; NS, not significant; NA, not applicable; W/H, waist-to-hip ratio; Δ₄-A, Δ₄-androstenedione; α-OHP, 17α-hydroxyprogesterone; SHBG, sex hormone-binding globulin; QUICKI, quantitative insulin sensitivity check index. ***post hoc* tests between patients with different types of menstrual cycle irregularities. Significant differences in the *post hoc* comparisons between patients with regular and irregular cycles: **P*<0.001; †*P*<0.005; ‡*P*<0.01; and §*P*<0.05.

Table 3 Characteristics of women with PCOS and multiple cycle irregularities and of women with PCOS and regular menstrual cycles (RMC).

	n	SA+OM	SA+PM	OM+PM	RMC	P (overall)	P**	
							SA+OM vs SA+PM	SA+OM vs OM+PM
Age (years)	82	23.6±5.7 [§]	23.6±4.4	23.8±5.6 [§]	131	0.011	NS	NS
BMI (kg/m ²)		26.8±7.0	25.6±6.9	25.9±7.3	25.7±5.7	NS	NA	NA
Waist (cm)		83.9±16.9	82.6±15.1	82.1±15.9	26.6±5.6	NS	NA	NA
W/H		0.78±0.08	0.78±0.05	0.78±0.06	82.0±11.8	NS	NA	NA
FSH (IU/l)		5.5±1.7 [†]	6.1±1.8	5.8±1.8	0.77±0.06	NS	NA	NA
LH (IU/l)		8.8±5.2 [†]	11.8±10.7 [*]	8.1±5.4 [†]	6.2±1.7	0.035	NS	NS
Prolactin (ng/ml)		11.9±6.3 [†]	16.4±7.7	14.1±7.1	6.1±3.9	<0.001	NS	NS
Testosterone (nmol/l)		74.6±33.1	89.2±42.2	71.9±28.6	14.7±6.9	0.003	0.005	0.016
Δ ₄ -A (nmol/l)		3.0±1.4	2.9±1.3	2.7±0.9	73.6±27.3	NS	NA	NA
DHEAS (μg/l)		2890.8±1200.5	3666.2±1838.7	2907.8±1219.2	2.8±1.1	NS	NA	NA
FAI		9.36±8.21	11.25±8.78 [†]	6.77±4.30	3158.3±1319.9	0.017	0.011	NS
17α-OHP (nmol/l)		1.2±0.5	1.2±0.4	1.1±0.6	7.52±4.37	<0.001	NS	0.006
SHBG (nmol/l)		41.3±25.3	44.9±46.0	46.9±25.6	1.1±0.6	NS	NA	NA
Glucose (mmol/l)		96.9±11.8	95.6±11.4	98.6±11.1	42.7±23.6	NS	NA	NA
Insulin (pmol/l)		13.8±13.0	13.7±22.6	11.4±7.8	96.5±11.5	NS	NA	NA
Glucose/insulin		12.41±8.26	13.32±6.99	11.77±6.28	10.4±6.4	NS	NA	NA
AUC glucose-OGTT		15 105.2±3097.1	16 118.2±3657.3	15 465.5±3140.3	12.57±7.65	NS	NA	NA
HOMA-IR		3.37±3.21	3.19±5.15	2.82±1.98	15 029.4±2577.6	NS	NA	NA
QUICKI		0.34±0.03	0.35±0.03	0.34±0.03	2.52±1.64	NS	NA	NA
Ovarian volume (cm ³)		9.9±4.3 [†]	8.7±4.4	9.5±5.7 [†]	0.34±0.03	NS	NA	NA
Ovarian follicles		12.4±4.7	10.9±3.5	12.4±8.2	8.1±3.4	0.014	NS	NS
					11.8±3.9	NS	NA	NA

OM, oligomenorrhea; SA, secondary amenorrhea; PM, polymenorrhea; NS, not significant; NA, not applicable. ***post hoc* tests between patients with different types of menstrual cycle irregularities. Significant differences in the *post hoc* comparisons between patients with regular and irregular cycles: **P*<0.001; †*P*<0.005; ‡*P*<0.01; and §*P*<0.05.

secondary amenorrhea or with regular menstrual cycles did not differ in markers of IR from Group D. Two previous smaller studies ($n=72$ and $n=418$ respectively) reported that patients with PCOS and oligomenorrhea or amenorrhea had more severe IR than patients with PCOS and regular cycles (10, 11). However, the latter studies did not differentiate between patients with oligomenorrhea and amenorrhea (10, 11). In contrast, in two more recent small studies ($n=184$ and $n=118$ respectively) that analyzed patients with amenorrhea separately from patients with oligomenorrhea, only the former had more pronounced IR than patients with regular menses (12, 13). Markers of IR did not differ between patients with oligomenorrhea and patients with regular menses (12, 13). We also observed that women with regular menstrual cycles alternating with secondary amenorrhea were more insulin resistant than women with regular menstrual cycles alternating with oligomenorrhea. There are no studies that compared markers of IR between different types of menstrual abnormalities in patients with PCOS. Overall, our findings suggest that amenorrhea is a useful marker of IR in patients with PCOS whereas oligomenorrhea does not imply more severe IR. This association is possibly explained by the relationship between IR and anovulation. Indeed, most patients with PCOS and amenorrhea are anovulatory and IR contributes to the pathogenesis of anovulation in PCOS by aggravating hyperandrogenemia and by inducing ovarian follicular arrest (1, 2). Therefore, the more severe IR might partly explain the presence of amenorrhea in these patients. On the other hand, patients with oligomenorrhea might have less perturbed ovulation partly because they have less severe IR. Interestingly, a recent study showed that the hormonal/metabolic profile is comparable in women with PCOS despite the time of menstrual irregularities occurrence (20). This observation and our findings in this study suggest that the type of menstrual irregularity might be more important than the duration of PCOS in determining the metabolic profile of these women.

This is the first study that assessed the association between polymenorrhea and the metabolic and endocrine characteristics of patients with PCOS. We observed that patients with polymenorrhea alone or in combination with other cycle abnormalities or alternating with regular menstrual cycles did not differ in markers of IR from Group D. Moreover, patients with regular menstrual cycles alternating with polymenorrhea were less insulin resistant than patients with regular menstrual cycles alternating with either secondary amenorrhea or oligomenorrhea. These results suggest that polymenorrhea is associated with milder impairment in glucose metabolism than amenorrhea and oligomenorrhea. Indeed, in the general population, women with oligomenorrhea appear to have increased risk for T2DM whereas those with polymenorrhea have an incidence of T2DM similar to women with regular

menses (20). However, when clinical signs of hyperandrogenemia (hirsutism and/or acne) were present in women with polymenorrhea, the risk of T2DM increased (21). Clearly, more studies are required to confirm or refute the relationship between polymenorrhea and IR/T2DM and to clarify the mechanism(s) underpinning this association.

Differences in circulating androgens paralleled differences in markers of IR. Indeed, patients with primary or secondary amenorrhea or oligomenorrhea had more severe hyperandrogenemia than Group D whereas patients with polymenorrhea had a similar degree of hyperandrogenemia with the latter. A previous study reported higher androgen levels in patients with either amenorrhea or oligomenorrhea than in those with normal cycles (13) whereas another did not detect any differences in androgen levels between the three groups, possibly because of limited statistical power (12). Therefore, it appears that the severity of menstrual abnormality also reflects the degree of hyperandrogenemia. Indeed, ovarian hyperandrogenism is associated with anovulation in PCOS by inducing ovarian follicular arrest (2, 22). Accordingly, the type of menstrual cycle irregularity might also represent an inexpensive and easily determined marker of hyperandrogenemia in patients with PCOS.

In conclusion, amenorrhea is associated with more pronounced IR and hyperandrogenemia in patients with PCOS. Oligomenorrhea portends a less excessive risk for these abnormalities than amenorrhea whereas polymenorrhea appears to be even more benign metabolically. Therefore, the type of menstrual cycle abnormality might represent a useful tool for identifying a more severe metabolic profile in PCOS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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