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Metabolic profile in women with polycystic ovary syndrome across adult life

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ABSTRACT

Objective. To assess insulin sensitivity, insulin secretion and metabolic profile in women with polycystic ovary syndrome (PCOS) in different stages of reproductive life.

Materials and methods. In a cross-sectional study, 190 PCOS women (PCOSw) and 99 controls (Cw) aged between 18 and 55 years were included. PCOSw and Cw were distributed into 3 stages of reproductive life: early reproductive age (18–34 years old), late reproductive age (35–40 years old) and perimenopausal period (41–55 years old). Waist circumference (WC), body mass index (BMI) and blood pressure (BP) were recorded. An oral glucose tolerance test (OGTT) with measurement of glucose and insulin was performed. Sex steroids and lipid profile were also determined in the fasting sample. Insulin sensitivity was assessed by HOMA-IR and ISI composite, and insulin secretion by HOMA-β and insulinogenic index. Visceral adiposity index (VAI) and lipid accumulation product (LAP) were also calculated. Metabolic syndrome (MS) was assessed by the IDF and ATPIII criteria.

Results. At early reproductive age, PCOSw showed higher BMI, WC, and VAI and a higher prevalence of MS compared to Cw ($p < 0.05$). In addition, at late reproductive age PCOSw also showed elevated total cholesterol, triglycerides, insulin secretion, LAP and BP. At perimenopausal period, these parameters were not different between Cw and PCOSw. Within the PCOSw group, HOMA-β was lower at late reproductive and perimenopausal periods compared to the early reproductive age. Regarding control women, a deterioration of anthropometric and metabolic parameters was observed in perimenopausal women compared to early and late reproductive women.

Abbreviations: PCOS, polycystic ovary syndrome; IR, insulin resistance; WHR, waist to hip ratio; BP, blood pressure; BMI, body mass index; OGTT, oral glucose tolerance test; WC, waist circumference; HOMA-IR, homeostasis model assessment for insulin resistance; ISI composite, insulin sensitivity index composite; VAI, visceral adiposity index; LAP, lipid accumulation product; MS, metabolic syndrome; IDF, International Diabetes Federation; ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NIH, National Institutes of Health; FAI, free androgen index; ADA, American Diabetes Association; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; AUC, area under the curve; OR, odds ratio.

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Conclusions. Our results suggest that metabolic derangements associated with PCOS are more evident at the early and late reproductive ages. On the other hand, during perimenopause, there is no further deterioration of metabolic parameters. Nevertheless, a disruption in pancreatic β-cell function is evidenced at this stage.

1. Introduction

Polycystic ovary syndrome (PCOS) is a well-recognized endocrine-metabolic disturbance affecting 6% to 20% of women in fertile age, depending on the diagnostic criteria employed [1]. Insulin resistance (IR) is present in about 50–70% of PCOS patients independent of body mass index (BMI) [2,3]. Moreover, metabolic syndrome (MS) components such as abdominal obesity, dyslipidemia, hyperglycemia and hypertension, are highly prevalent in women with PCOS, predisposing them to the development of type 2 diabetes and cardiovascular disease [4,5].

In normal women, the menopausal transition increases the prevalence of components of MS [6]. This has been associated with a decrease in ovarian function, leading to a decrease in estrogen synthesis and a redistribution of fat to the abdominal depot [7].

In PCOS women, metabolic abnormalities begin early in life and are worsened by the presence of hyperandrogenism [8]. However, the evolution of MS components with advanced age has not been thoroughly explored.

Cross-sectional retrospective studies have shown that the risk of developing an adverse metabolic profile in PCOS women increases during the perimenopausal and menopausal periods [9,10]. In contrast, recently, a longitudinal study showed that hyperandrogenic women with menstrual disorders do not increase their rate of MS, stroke or myocardial infarction when they reach the perimenopausal period [11]. We have suggested that PCOS women maintain their ovarian steroidogenic activity during late reproductive age [12]. However, it is not known if these changes have an impact on the MS associated with PCOS. Therefore, the aim of the present study was to evaluate IR and MS components during the perimenopausal period compared to reproductive life.

2. Materials and methods

2.1. Subjects

One hundred ninety PCOS women (PCOSw) and 99 controls (Cw) between 18 and 55 years of age, with a BMI ranging from 20 to 35 kg/m^2, were included in this study. Women were distributed into 3 stages of reproductive life: early reproductive age (18–34 years old), late reproductive age (35–40 years old) and perimenopausal period (41–55 years old). PCOS women were diagnosed in our Research Unit (1990 to 2014) according to the NIH consensus criteria when the patients were in the early reproductive age.

Control women (Cw) were selected from women attending the preventive medical examination at the Department of Obstetrics and Gynecology in our hospital, as previously described (12). Women who had a history of regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and no history of infertility or pregnancy complications, were included.

More details are shown in the supplementary materials.

2.2. Study protocol

Control and PCOS subjects were studied 3 to 7 days after menstrual bleeding or whenever feasible in women without regular menses. We performed a complete physical examination with anthropometric measurements including: weight, height, waist circumference (WC), waist to hip ratio (WHR), body mass index (BMI) and blood pressure (BP).

Baseline serum concentrations of testosterone, androstenedione, estradiol and sex hormone binding globulin (SHBG) were determined and free androgen index (FAI) was calculated. In all participants, an oral glucose tolerance test (75 g glucose) was performed after a 12-h overnight fast. Glucose tolerance was evaluated by using the criteria of the American Diabetes Association (ADA). A lipid profile was determined in the fasting sample.

2.3. Surrogate measurements: Insulin sensitivity, β-cell function and adiposity

Insulin resistance was estimated by the homeostasis model assessment for IR (HOMA-IR) and by the insulin sensitivity index (ISI) composite. To assess β-cell function, insulinogenic index and HOMA-β were calculated. Total glucose and insulin secretions were determined as the area under the curve. Lipid accumulation product (LAP) and visceral adiposity index (VAI) were estimated.

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III definition and according to the International Diabetes Federation (IDF) criteria.

More details are described in the supplementary material section.

2.4. Statistical evaluation

Data are expressed as median and interquartile range because they are not normally distributed according to the Shapiro–Wilk test. For comparisons between two groups, a Mann–Whitney test was performed. Differences between groups were adjusted by ANCOVA using age or BMI. Comparisons along the different age periods were performed by the Kruskal–Wallis test followed by Dunn's test. A chi-square test of independence was used for comparisons of categorical variables. Associations between sex steroids and metabolic variables were determined using the Spearman correlation coefficients test. A generalized linear model (GLM) with gamma distribution and log-link function

was utilized to control for baseline differences between Cw and PCOSw with age as a continuous scale, using a non-parametric analysis [13]. Statistical analysis was performed using the STATA 13.0, SPSS 22.0 and GraphPad Prism 6.0 packages. We used a 5% significance level.

3. Results

3.1. Clinical and biochemical characteristics

As expected, Ferriman–Gallwey score, androgen levels and FAI were higher in the PCOS group. These differences remained significant after adjusting for age (Supplementary Table 1).

Clinical characteristics in Cw and PCOSw at the 3 study periods are shown in Table 1. Age was similar between both groups within each study period. Weight was higher in PCOSw at the early reproductive age and the perimenopausal period. BMI was higher in PCOSw only during early reproductive age, tended to be higher at late reproductive age ($p = 0.054$) and was comparable at the perimenopausal period.

WC and hip circumference were higher in PCOSw compared to Cw at early and late reproductive ages, while WHR was higher in PCOSw only at the early reproductive age. These parameters became comparable between both groups at the perimenopausal period.

At late reproductive age, PCOSw showed higher BP compared to Cw. Only systolic BP remained higher in PCOSw after adjusting for BMI ($p = 0.023$). There were no significant differences in BP in the other periods.

Considering each group along the different age periods, in control women, BMI, WC and WHR were significantly higher in the perimenopausal period compared to early reproductive age. On the other hand, BP was higher in perimenopause compared to late reproductive age ($p < 0.05$). In PCOSw these parameters remained constant along the 3 periods.

3.2. Metabolic characteristics, insulin sensitivity and insulin secretion

Comparisons between Cw and PCOSw with unadjusted p values are shown in Table 2. After adjusting for BMI, VAI was higher in early reproductive PCOSw compared to Cw ($p = 0.005$). In the late reproductive period, total cholesterol ($p = 0.028$), triglycerides ($p = 0.011$), post-load insulin ($p = 0.018$), AUC insulin ($p = 0.003$), LAP ($p = 0.014$) and VAI ($p = 0.023$) were significantly higher, with a trend to higher fasting glucose ($p = 0.068$) and insulinogenic index ($p = 0.051$), in PCOSw compared to Cw. In the perimenopausal period, AUC insulin was higher in PCOSw compared to Cw ($p = 0.022$).

Comparisons within each group along the different age periods are also shown in Table 2. In Cw, total cholesterol was higher in the perimenopausal period compared to early and late reproductive ages; whereas triglycerides, LAP and VAI were higher in perimenopause compared to the early reproductive period. Moreover, HOMA-β tended to be higher during the perimenopausal stage compared to the other two periods.

In PCOSw, fasting glucose, total cholesterol and LDL-cholesterol increased and fasting insulin decreased from the early to the late reproductive period. Of interest, HOMA-β was higher at the early reproductive age compared to the other periods. LAP and VAI remained constant during the 3 age categories.

In order to verify the age related changes of all parameters in the PCOS group (taking Cw as the normal condition), we performed a generalized linear model which showed that WHR, AUC glucose and VAI increased, whereas fasting insulin and AUC insulin decreased, in PCOSw ($p < 0.05$).

3.3. Association of sex steroids and metabolic parameters

In PCOSw, at early reproductive age, FAI showed a positive correlation with WC ($r = 0.310$, $p = 0.001$), triglycerides ($r = 0.214$, $p = 0.025$), AUC glucose ($r = 0.263$, $p = 0.006$), AUC insulin ($r = 0.315$, $p = 0.001$) and LAP ($r = 0.302$, $p = 0.001$), and a negative correlation with ISI composite ($r = -0.321$, $p = 0.001$). No correlations were observed in Cw at any of the periods studied (data not shown).

3.4. Metabolic syndrome

PCOSw exhibited a significantly higher prevalence of MS compared to Cw at early (5.3 v/s 24.8 by ATPIII and 5.3 v/s 34.2 by IDF) and late reproductive ages (5.3 v/s 37.2 by ATPIII and 15.8 v/s 46.5 by IDF) according to both criteria. At the perimenopausal period, the prevalence was comparable. Odds ratio (OR) for MS, for the whole PCOS group, was 3.46 (CI: 1.66–7.21, $p = 0.001$) according to the ATP III criteria and 3.43 (CI: 1.80–6.53, $p < 0.001$) according to the IDF criteria; with a 95% confidence interval. MS components are shown in Supplementary Table 2.

4. Discussion

At early and late reproductive ages, women with PCOS showed derangements in anthropometric and metabolic parameters and a higher prevalence of metabolic syndrome compared to control women. Interestingly during the perimenopausal period, these parameters were not different between control and PCOS women. Higher prevalence of MS has been reported in women with PCOS compared to control women with the OR for metabolic disturbances two to four times higher [4], which is similar to this study. On the other hand, Panidis et al. reported that only women with PCOS aged over 30 years were more obese and had higher prevalence of MS than control women [14].

In our study, early and late reproductive age PCOSw had higher VAI and LAP, surrogate indicators of visceral adiposity and metabolic disturbances, promoting a proinflammatory state leading to the development of IR, which is in agreement with previous reports [15].

Even more, total cholesterol and LDL-cholesterol levels increase in PCOSw during late reproductive age, suggesting that aging imposes a deleterious metabolic impact. Along with these changes, women with PCOS show an increase in the prevalence of hypertension. However at this age, the reduction in fasting insulin and HOMA-β and the increase in fasting glucose compared to the early reproductive period, suggest an incipient impairment of β-pancreatic function which is no longer able to fully compensate the IR state observed in these patients [16].

Table 1 – Comparison of clinical characteristics in control and PCOS women across the three study periods. [a]

	Early reproductive age (18–34 years)			Late reproductive age (35–40 years)			Perimenopause (41–55 years)		
	Cw (n = 19)	PCOSw (n = 117)	Unadjusted p value	*Cw* (n = 38)	PCOSw (n = 43)	Unadjusted p value	*Cw* (n = 42)	PCOSw (n = 30)	*Unadjusted p value*
Age (years)	29 (20–30)	27 (23–30)	0.755	37 (36–38)	36 (35–38)	0.067	47 (43–52)	47 (43–49)	0.535
Weight (kg)	58 (54–69)	69 (61–78)	0.005	63 (56–68)	65 (60–76)	0.074	65 (60–69)	69 (63–76)	0.026
Height (m)	1.61 (1.57–1.62)	1.59 (1.55–1.63)	0.479	1.57 (1.54–1.61)	1.57 (1.52–1.64)	0.909	1.56 (1.50–1.62)	1.60 (1.57–1.65)	0.017
BMI (kg/m^2)	23.1 (21.5–26.4)	26.9 (24.0–30.8)	0.002	26.0 (23.1–27.9)	27.0 (24.7–29.7)	0.054	26.8 (24.4–29.6) [a]	26.4 (24.1–31.5)	0.964
WC (cm)	73 (68–79)	82 (77–92)	0.002	81 (73–86)	84 (80–94)	0.019	79 (76–90) [a]	84 (77–93)	0.134
Hip circumference (cm)	93 (86–101)	99 (93–105)	0.029	93 (90–100)	98 (92–106)	0.040	96 (93–103)	101 (95–107)	0.120
Waist to hip ratio	0.79 (0.77–0.85)	0.84 (0.81–0.88)	0.004	0.85 (0.79–0.90)	0.86 (0.82–0.91)	0.156	0.84 (0.80–0.89) [a]	0.85 (0.80–0.87)	0.749
Waist to height ratio	0.46 (0.44–0.49)	0.52 (0.48–0.57)	0.001	0.51 (0.46–0.55)	0.55 (0.51–0.59)	0.013	0.52 (0.49–0.56) [a]	0.52 (0.48–0.58)	0.780
Systolic BP (mm Hg)	110 (100–120)	110 (100–120)	0.760	110 (100–120)	120 (110–120)	0.006	120 (110–120) [b]	120 (110–120)	0.831
Diastolic BP (mm Hg)	70 (60–70)	70 (60–80)	0.441	60 (60–70)	70 (60–75)	0.035	70 (70–80) [b]	70 (65–75)	0.617

Results are expressed as median and interquartile range. BMI: body mass index; WC: waist circumference, BP: blood pressure.
Table shows unadjusted p values between Cw and PCOSw in each age category.
[a] $p < 0.05$ between early reproductive age and perimenopause in Cw.
[b] $p < 0.05$ between late reproductive age and perimenopause in Cw.

Table 2 – Comparison of metabolic characteristics and surrogate measurements of insulin secretion and insulin sensitivity in control and PCOS women across the three study periods. [e]

	Early reproductive age (18–34 years)			Late reproductive age (35–40 years)			Perimenopause (41–55 years)		
	Cw (n = 19)	PCOSw (n = 117)	Unadjusted p value	*Cw* (n = 38)	PCOSw (n = 43)	Unadjusted p value	*Cw* (n = 42)	PCOSw (n = 30)	*Unadjusted p value*
Fasting									
Glucose (mg/dl)	85 (76–98)	82 (75–90)	0.265	81 (76–91)	87 (81–96) [c]	0.068	84 (76–89)	89 (79–93)	0.158
Insulin (μUI/ml)	8.4 (7.2–13.8)	12.8 (7.8–19.5)	0.088	9.9 (7.6–11.9)	9.7 (6.0–14.6) [c]	0.787	10.0 (7.1–12.3)	10.0 (5.5–11.6)	0.527
HOMA-β	162 (115–267)	270 (146–403)	0.043	172 (135–253)	152 (109–256) [c]	0.310	191 (121–268)	155 (101–251) [d]	0.407
HOMA-IR	1.9 (1.4–3.1)	2.5 (1.5–4.2)	0.116	2.0 (1.5–2.6)	2.0 (1.2–3.3)	0.644	1.9 (1.5–2.6)	2.0 (1.1–2.4)	0.816
Total cholesterol (mg/dl)	163 (150–183)	167 (143–198)	0.814	169 (150–189.)	186 (163–209) [c]	0.023	189 (168–218) [a, b]	187 (172–215)	0.861
LDL-cholesterol (mg/dl)	106 (91–118)	96 (77–125)	0.354	101 (91–119)	115 (93–141) [c]	0.087	120 (95–147)	122 (94–136)	0.921
HDL-cholesterol (mg/dl)	41.9 (37.6–46.7)	41.5 (34.4–48.9)	0.930	45.6 (38.2–50.5)	42.8 (33.6–49.8)	0.287	44.0 (37.2–53.1)	42.0 (38.2–53.2)	0.848
Triglycerides (mg/dl)	92 (71–127)	145 (102–177)	0.001	98 (81–129)	138 (91–184)	0.007	128 (93–171) [a]	135 (91–170)	0.667
Post-load									
Glucose (mg/dl)	92 (84–106)	100 (85–124)	0.314	104 (88–118)	99 (82–123)	0.687	101 (87–122)	111 (92–124)	0.407
Insulin (μUI/ml)	37.9 (26.2–61.2)	73.4 (41.4–138.6)	0.008	34.1 (21.0–61.8)	65.7 (27.8–116.4)	0.026	42.2 (34.3–68.3)	50.3 (25.2–105.4)	0.579
Insulinogenic index	1.1 (0.8–2.7)	2.1 (1.1–3.7)	0.111	1.2 (0.4–1.8)	1.7 (1.0–3.7)	0.014	1.3 (0.8–2.1)	1.6 (0.7–3.5)	0.642
ISI composite	5.7 (3.2–8.3)	3.6 (2.0–6.2)	0.027	6.1 (4.2–7.8)	4.3 (2.8–6.5)	0.034	5.3 (4.2–6.4)	4.6 (3.3–7.6)	0.478
AUC glucose	12,870 (10,650–13,905)	13,087 (11,182–16,005)	0.252	12,502 (10,991–14,902)	13,770 (11,685–16,200)	0.151	12,585 (11,310–15,555)	13,515 (11,962–15,562)	0.305
AUC insulin	5438 (3613–9149)	9359 (5767–16,410)	0.006	5350 (3485–7478)	8868 (5338–13,942)	0.002	5542 (4226–8101)	7049 (3816–10,678)	0.236
Adiposity indexes									
LAP	17.3 (8.8–28.1)	40.2 (22.5–62.3)	<0.001	23.8 (18.0–35.6)	38.5 (24.7–62.3)	0.001	31.2 (18.2–56.5) [a]	41.7 (23.9–63.7)	0.275
VAI	2.0 (1.5–2.2)	2.9 (2.0–3.7)	0.001	2.2 (1.7–3.1)	2.9 (2.3–3.8)	0.010	2.9 (2.1–3.8) [a]	3.4 (2.3–4.3)	0.317

Results are expressed as median and interquartile range. LAP: lipid accumulation product; VAI: visceral accumulation index.
Table shows unadjusted p values between Cw and PCOSw in each age category.

[a] $p < 0.05$ between early reproductive age and perimenopause in Cw.
[b] $p < 0.05$ between late reproductive age and perimenopause in Cw.
[c] $p < 0.05$ between early and late reproductive age in PCOSw.
[d] $p < 0.05$ between early reproductive age and perimenopause in PCOSw.
[e] $p < 0.05$ between late reproductive age and perimenopause in PCOSw.

At the perimenopausal period, Cw and PCOSw showed the same anthropometric and metabolic features, indicating that the metabolic profile did not worsen when women with PCOS reached the perimenopausal period. In this regard, a recent longitudinal study showed that components of MS and risk for cardiovascular events did not increase during the perimenopausal period in women with a history of hyperandrogenism and anovulation [11], although the results are still controversial [9,10].

In the present study, perimenopausal control women showed a disturbed body fat distribution reflected by an increase in waist circumference, waist to hip ratio, VAI and LAP. Clinical evidence suggests that the lower estrogen levels associated with cessation of ovarian function and the relatively elevated testosterone levels cause a deterioration of body composition, which may explain some of the alterations observed in women at this age [7,17–19]. The deterioration of anthropometric and metabolic parameters observed in perimenopausal control women, may be explained by the development of an extrinsic IR as a consequence of a physiological aging phenomenon.

On the other hand, a recent study showed that there is an intrinsic IR in PCOS, which can be aggravated by exogenous conditions such as weight and lifestyle as noted in young women [2]. It is important to mention that in PCOSw, fasting glucose increased with age which is concordant with the concept that women with PCOS carry a higher risk for developing diabetes than control women as has been previously suggested [20].

The present study does not have a prospective design, which could be a limitation in the interpretation of the results. Nevertheless, the generalized linear model analysis was used to overcome this limitation, allowing us to establish that insulin secretion decreased with age in the PCOS condition. We can also suggest that age along with obesity appear to be better predictors of metabolic abnormalities in PCOSw than the presence of the syndrome *per se*. A strength of the study is that all patients belong to a very well characterized cohort of PCOS patients which have been followed for many years since their initial diagnosis.

In summary, our results suggest that metabolic derangements associated with PCOS are more evident at the early and late reproductive ages, without a further deterioration of metabolic parameters during perimenopause. Nevertheless, a disruption in pancreatic β-cell function is evidenced at this later stage. Additionally, we corroborate the concept that PCOS has an intrinsic IR that persists in time, while in the control group there is an extrinsic IR that appears at later stages, giving a metabolic pattern similar to that of older PCOS women. Further follow-up studies in the late postmenopausal period are needed in order to confirm whether these women actually develop cardiovascular events and full metabolic disorders. Moreover, prospective studies should be performed to confirm the findings of cross-sectional studies.

Author Contributions

T.S.-P. and F.P.-B. designed and conducted the study. C.R., A.C., A.L.de.G. and P.H. participated in data collection and analysis. G.C. performed the statistical analysis. B.E., M.M. and N.C. analyzed the data and wrote the manuscript.

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Conflict of Interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2016.01.006.

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