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Short communication

Implications of the 2014 Androgen Excess and Polycystic Ovary Syndrome Society guidelines on polycystic ovarian morphology for polycystic ovary syndrome diagnosis

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A B S T R A C T

The Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS) has recommended an updated threshold for polycystic ovarian morphology (PCOM) of 25 follicles or more, 10 ml or more of ovarian volume, or both. We describe the effect of these guidelines on reproductive and metabolic characteristics in 404 women. These women were separated into four groups: group A: hyperandrogenism and oligo-amenorrhoea (n = 157); group B: hyperandrogenism or oligo-amenorrhoea and PCOM meeting AEPCOS 2014 criteria (n = 125); group C: hyperandrogenism or oligo-amenorrhoea and PCOM meeting Rotterdam 2003 but not AEPCOS 2014 criteria (n = 72); and group D: non-PCOS not meeting either criteria (n = 50). Groups B, C and D did not differ across any metabolic markers. The AEPCOS 2014 guidelines may have limited utility in distinguishing metabolic risk factors and result in the exclusion of a large group of oligo-anovulatory women.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder originally characterized by Stein and Leventhal in 1935 by the presence of amenorrhoea associated with bilateral polycystic ovaries (Dewailly et al., 2014). Since then, definitions for polycystic ovarian morphology (PCOM) have evolved. The most widely used 'Rotterdam criteria' for diagnosing PCOS defined PCOM by a threshold of 12 or more follicles throughout the entire ovary (FNPO), an ovarian volume of 10 ml

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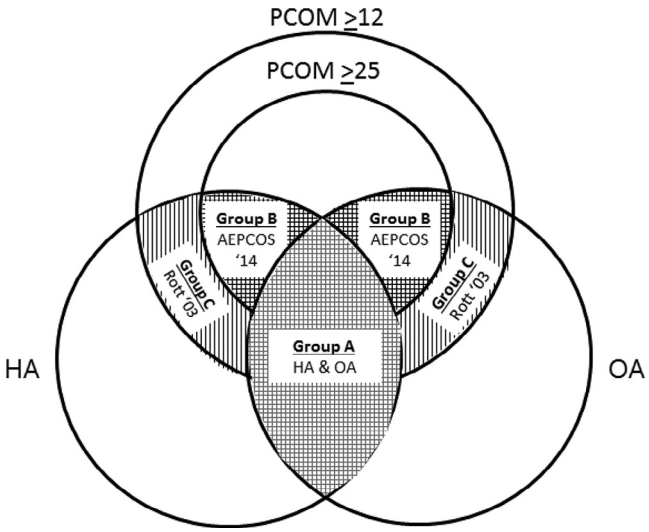

Figure 1 – Comparison of Rotterdam 2003 and Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS) 2014 guidelines for polycystic ovarian morphology when diagnosing polycystic ovary syndrome. Group C: Rott '03' is equivalent to the new Non-PCOS group referenced in Table 1. All non-shaded regions represent Group D (original non-PCOS). Comparisons are made between Groups A (*n* = 157); B (*n* = 125); C (*n* = 72); and D (*n* = 50) in Table 1. 398 women had OA, 161 had HA, 112 met Rott 2003 PCOM criteria but not AEPCOS 2014 criteria, 223 met AEPCOS 2014 PCOM criteria. PCOS, polycystic ovary syndrome; HA, hyperandrogenism; OA, oligio-amenorrhea; Rott, Rotterdam; PCOM, polycystic ovarian morphology.

or over (Dewailly et al., 2014), or both. Advances in ultrasound technology have improved discrimination between follicles and detection of smaller follicles. The use of newer technology with the original Rotterdam thresholds has resulted in an increase in the reported prevalence of PCOM among healthy women and left some to question the utility of this finding in diagnosing PCOS (Johnstone et al., 2010). The AEPCOS society recently reviewed the appropriateness of threshold definitions and released a task force recommendation that PCOM be defined as an FNPO 25 or over (rather then 12), an ovarian volume of 10 ml or over, or both (Dewailly et al., 2014).

Applying these new thresholds results in the reclassification of women with PCOS who have either hyperandrogenism or oligo-amenorrhoea, but not both. Using the more exclusive AEPCOS guidelines only those with 25 FNPO or over, an ovarian volume of 10 ml or more, or both, will meet criteria for PCOS, whereas those diagnosed with PCOS by the Rotterdam 2003 criteria with 12–25 follicles will now be considered non-PCOS (**Figure 1**). The reclassification of women based on these criteria will likely affect the reproductive and metabolic phenotype of women with PCOS, as ovarian morphology has been found to reflect markers of reproductive and metabolic derangement (Christ et al., 2015). Recently, this was corroborated by Quinn et al., who found that those women excluded from PCOS diagnosis by the AEPCOS 2014 criteria have elevated total cholesterol and more severe markers of insulin resistance than controls (Quinn et al., 2016). It still remains unclear, however, how these thresholds influence features among women with only one additional criterion for PCOS. The primary objective of this study was, therefore, to identify variations in markers of reproductive and metabolic disease using updated threshold definitions for PCOM in a population defined by normogonadotrophic anovulatory infertility initially diagnosed with PCOS according to the Rotterdam criteria (Dewailly et al., 2014).

Materials and methods

Women were included from a prospective cohort study involving extensive standardized initial screening conducted at the University Medical Center, Utrecht, as described in detail elsewhere (Daan et al., 2014). Between 2006 and 2016, a total of 1584 women were screened. Women were required to be fasting and aged 18–45 years to be eligible for screening. Of the 1584 women screened, 1057 met criteria for PCOS. To reduce the effect of variation between sonographers, only those women (*n* = 482) evaluated by the four trained sonographers at UMC Utrecht, which had seen the greatest number of patients were included. Therefore, of the 1057 women who met criteria for PCOS, 575 were excluded for this reason. No significant differences were found in FNPO between observer among PCOS and non-PCOS (data not shown). Furthermore, 78 women were excluded because insufficient data were available to assign PCOS phenotype.

Diagnosis of PCOS was assigned according to the Rotterdam-2003 criteria as previously described (Daan et al., 2014). Women were separated into four groups: group A: PCOS with hyperandrogenism and oligo-amenorrhoea; group B: PCOS with PCOM meeting AEPCOS (FNPO ≥25, ovarian volumne ≥10 ml, or both) criteria plus either hyperandrogenism or oligo-amenorrhea; group C: PCOS with PCOM meeting Rotterdam 2003 (FNPO 12–25) but not AEPCOS 2014 criteria plus either hyperandrogenism or oligo-amenorrhea; group D: non-PCOS not meeting either criteria for PCOS.

Women screened that did not meet criteria for diagnosis of PCOS or other causes of menstrual irregularities were identified as non-PCOS.

Transvaginal ultrasound scans were carried out using a 7.5 MHz transducer on an ALOKA Prosound 6 system to assess ovarian volume and FNPO 2–10 mm. Reproductive and metabolic parameters were obtained for each participant as described previously (Daan et al., 2014).

Variables were compared between groups with one-way analysis of variance with post-hoc Tukey's honest significant difference test. Non-normally distributed data were transformed with Box-cox Y transformation before analysis.

All study procedures were initially approved by the local Institutional Ethical Review Board on December 28, 2004 (reference number 04/263) and for continuing analysis of the data on 18 January 2012 (reference number 12–618/C). Written informed consent was obtained from all participants. International trial registry number NCT02309047.

Results

A total of 404 women met inclusion criteria for this study based on the Rotterdam criteria for diagnosing PCOS. At the time of screening, three women had a recorded history of diabetes mellitus type 2 and 46 women met criteria for hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg). A total of 157 women had both hyperandrogenism and oligo-amenorrhoea (Group A). Among those with only PCOM and one additional criterion, 125 met AEPCOS 2014 (Group B) and 72 met Rotterdam 2003

Table 1 – Variations in reproductive and metabolic markers between new polycystic ovary syndrome classifications.

	Group A HA and OA (n = 157)	Group B AEPCOS 2014 (HA or OA and PCOM 25+) (n = 125)	Group C Rotterdam 2003-New non-PCOS (HA or OA and PCOM 12–25) (n = 72)	Group D Original non-PCOS (n = 50)	P-value[e]
Polycystic ovarian morphology[f], n (%)	98 (62.42)	125 (100)	0 (0)	0 (0)	<0.0001
Hyperandrogenism[g] n (%)	157 (100)	3 (2.40)	1 (1.39)	0 (0)	<0.0001
Oligo-amenorrhea, n (%)	157 (100)	122 (97.60)	71 (98.61)	48 (96)	NS
FAI[h]	9.84 ± 17.57[a]	2.7 ± 1.19[b]	2.57 ± 1.04[b]	1.87 ± 0.82[c]	<0.0001
Hirsutism	5.73 ± 6.4[a]	1.23 ± 1.99[b]	1.45 ± 2.4[b,c]	0.4 ± 1.01[c]	<0.0001
Total testosterone (nmol/L)	2.33 ± 0.98[a]	1.68 ± 0.63[b]	1.41 ± 0.45[c]	1.02 ± 0.37[d]	<0.0001
SHBG (nmol/L)	33.10 ± 15.95[a]	68.20 ± 27.52[b]	62.32 ± 28.62[b]	62.30 ± 27.66[b]	<0.0001
DHEA (nmol/l)	24.33 ± 13.06[a]	18.11 ± 9.16[b]	19.07 ± 9.3[b]	15.17 ± 8.92[b]	<0.0001
Androstenedione (nmol/l)	8.57 ± 2.92[a]	6.18 ± 2.17[b]	5.25 ± 1.76[c]	3.82 ± 1.36[d]	<0.0001
FSH (IU/l)	6.28 ± 1.78[a,c]	5.85 ± 2[c]	6.7 ± 2.19[a,b]	7.2 ± 2.15[b]	0.0002
LH (IU/L)	10.1 ± 5.32[a]	7.7 ± 5.22[b]	7.2 ± 8.5[b,c]	4.99 ± 4.77[c]	<0.0001
BMI (kg/m^2)	29.44 ± 7.35[a]	24.05 ± 4.93[b]	23.43 ± 3.44[b]	23.89 ± 5.30[b]	<0.0001
Systolic BP (mmHg)	121.38 ± 12.88[a]	117.63 ± 13.18[a]	118.03 ± 12.01[a]	118.08 ± 13.91[a]	NS
Diastolic BP (mmHg)	77.79 ± 9.79[a]	74.77 ± 8.42[b]	74.57 ± 9.23[a,b]	76.58 ± 9.77[a,b]	0.0211
Insulin (mIU/l)	17.18 ± 30.35[a]	7.79 ± 5.42[b]	7.02 ± 4.34[b]	8.43 ± 6.57[b]	<0.0001
Glucose (mmol/l)	5.21 ± 0.74[a]	4.94 ± 0.39[b]	5.2 ± 1.02[a,b]	5.01 ± 0.56[a,b]	0.0019
Cortisol (umol/l)	0.25 ± 0.1[a]	0.25 ± 0.08[a]	0.26 ± 0.1[a]	0.27 ± 0.12[a]	NS
Triglycerides (mmol/l)	1.1 ± 0.65[a]	0.83 ± 0.42[b]	0.93 ± 0.81[a,b]	1.06 ± 1.04[a,b]	0.0105
Total cholesterol (mmol/l)	4.66 ± 0.84[a]	4.58 ± 0.94[a]	4.81 ± 0.98[a]	4.79 ± 1.15[a]	NS
HDL-C (mmol/l)	1.36 ± 0.35[a]	1.53 ± 0.35[b]	1.52 ± 0.31[b]	1.56 ± 0.36[b]	0.0002
LDL-C (mmol/l)	2.86 ± 0.69[a]	2.7 ± 0.84[a]	2.89 ± 0.85[a]	2.69 ± 0.77[a]	NS

Values expressed as mean ± SD or number and %. Across rows, groups with different superscript letters (a, b, c, or d) are significantly different as determined by Tukey's honest significant difference test ($P < 0.05$).

[e] *P*-value represents significant differences across groups via one-way analysis of variance or Pearson chi-square.

[f] PCOM is defined by AEPCOS 2014 criteria (Dewailly et al., 2014).

[g] Hyperandrogenism is defined as FAI >4.5, Ferriman–Gallwey score ≥9, or both.

[h] Free androgen index = (Total testosterone/SHBG) * 100.

ANSD, androstenedione; BP, blood pressure; DHEA, dehydroepiandrosterone; FAI, free androgen index; HA, hyperandrogenism; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OA, oligo-amenorrhoea; PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; SHBG, sex hormone binding globulin.

but not AEPCOS 2014 PCOM criteria (Group C). Fifty women were classified as original non-PCOS (Group D). When applying the AEPCOS criteria for PCOM, 122 were classified as non-PCOS (Group C + D).

Overall, significant differences across groups were found for FAI, hirsutism, testosterone, dehydroepiandrosterone, androstenedione, sex hormone binding globulin (all $P < 0.0001$), FSH ($P = 0.0002$), LH, body mas index (both $P < 0.0001$), diastolic blood pressure ($P = 0.0211$), insulin ($P < 0.0001$), glucose ($P = 0.0019$), triglycerides ($P = 0.0105$), and HDL-C ($P = 0.0002$) (**Table 1**). The AEPCOS-2014 group (Group B) had significantly greater total testosterone, androstenedione and significantly lower FSH than the Rotterdam-2003 (Group C) and original non-PCOS (Group D) groups ($P < 0.05$). No significant differences were observed across any metabolic parameters between AEPCOS 2014, Rotterdam 2003, or original non-PCOS groups.

Discussion

With the use of a large prospective cohort, the clinical implications of using the AEPCOS 2014 guidelines for PCOM were investigated. We focused on those women most affected by these guidelines (i.e. those with only one additional criterion for PCOS).

The application of these guidelines resulted in the reclassification of 72 (18%) women who originally met the Rotterdam-2003 criteria into what would now be considered non-PCOS normogonadotrophic, oligo-anovulatory infertility. This group as well as the original non-PCOS women had significantly lower levels of some androgens compared with the AEPCOS 2014 group. No differences were found, however, between these groups across any metabolic marker. The absolute differences in androgen levels between groups were small, which may explain the homogeneity in metabolic markers (Broekmans et al., 2006). Therefore, the AEPCOS 2014 guidelines seem to provide limited information about hyperandrogenism and metabolic disease, while excluding a group of anovulatory women from diagnosis that likely will still require similar ovulation induction for infertility management. Furthermore, the lack of difference in markers of metabolic dysfunction between groups B and C may suggest that surveillance for cardiovascular disease should focus on those women with both hyperandrogenism and oligo-amenorrhea (Group A).

The present study has several limitations. Because these data are part of a study recruiting women referred for evaluation of menstrual irregularities, few women exhibited hyperandrogenism, PCOM, or both, without oligo-amenorrhea. We are also limited in our ability to comment on infertility and obstetric management of these women.

Overall, our results provide evidence that the use of updated thresholds for PCOM using newer ultrasound equipment may provide limited added information concerning degree of hyperandrogenism, but does not provide additional information on cardiometabolic status and results in the exclusion of a large group of oligo-anovulatory women from PCOS diagnosis. Therefore, the utility of these new thresholds in women with only one additional criterion seems to be limited. Future longitudinal studies, however, will be required to further assess this question.

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