Extent of metabolic risk in adolescent girls with features of polycystic ovary syndrome

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Objective: To determine prevalence of metabolic syndrome in adolescents with polycystic ovary syndrome (PCOS) and derive features suggestive of propensity for development of metabolic syndrome.
Design: Prospective cohort study.
Setting: Population-based cohort of adolescents in Western Australia.
Participant(s): Metabolic data from 1,377 children aged 14 years, features of PCOS obtained from 244 girls aged 14 to 17 years.
Intervention(s): Assessment for features of PCOS and subsequent fasting blood samples.
Main Outcome Measure(s): Relationship between features of PCOS and features of metabolic syndrome.
Result(s): With use of five definitions of metabolic syndrome the maximal prevalence of metabolic syndrome recorded was 11.8% in girls with PCOS (National Institutes of Health [NIH]) and 6.6% (Rotterdam) (non-PCOS 0.6% and 0.7%, respectively). With use of cluster analysis of metabolic risk (a technique to cluster the adolescents according to multidimensional relationships of established cardiovascular risk factors), 35.3% with PCOS-NIH were at risk for metabolic syndrome and 26.2% with PCOS-Rotterdam (non-PCOS 15.4% and 15.4%, respectively). Menstrual irregularity and high free T (PCOS-NIH) were associated with high metabolic syndrome risk (odds ratio 3.00, confidence interval 1.3–6.4), not after controlling for body mass index. Of PCOS features, an elevated free T level was most predictive of insulin resistance. Menstrual irregularity and polycystic ovary morphology were not associated with insulin resistance (56.3% vs. 52.9% and 60.0% vs. 34.4%, respectively).
Conclusion(s): Despite the low prevalence of metabolic syndrome in girls with PCOS, one third have features putting them at high risk for development of metabolic syndrome. (Fertil Steril® 2011;■:■–■. ©2011 by American Society for Reproductive Medicine.)

Key Words: PCOS, adolescent, metabolic syndrome, Raine, hyperinsulinemia

The polycystic ovary syndrome (PCOS) is the commonest endocrine disorder of reproductive-aged women with a prevalence of approximately 5% to 8% in adults (1–3). However, the prevalence within an unselected population of adolescents may be as high as 31% (4). The syndrome is associated with metabolic derangements including obesity, hyperinsulinemia, impaired glucose tolerance, vascular reactivity, and inflammation (3, 5–10), posing a substantial health and economic burden to society (6). It is well established that obesity accentuates the clinical features of PCOS (3, 5, 7, 8). Centrally deposited fat is metabolically active, releasing inflammatory cytokines contributing to the adverse metabolic environment in PCOS (11).

Metabolic syndrome is a cluster of adverse cardiovascular features including central obesity, atherogenic dyslipidemia, insulin resistance (IR), a prothrombotic state, elevated blood pressure (BP), and increased circulating proinflammatory markers. Previous studies of the prevalence of metabolic syndrome in adolescents have been clinic based rather than population based and are at risk for bias (12–16). One population-based study reported higher insulin levels in adolescent girls with oligomenorrhea and polycystic ovaries (PCO) than in girls with oligomenorrhea with normal ovaries, concluded that it is doubtful that hyperinsulinemia is important in the development of PCO or PCOS, and proposed that hyperandrogenism precedes hyperinsulinemia (17). The aim of our study was to measure the prevalence of features of the metabolic

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syndrome in girls with PCOS in a representative sample of Western Australian children, to determine the features of PCOS that may predispose to features of metabolic syndrome in adolescence, and to derive early indicators of metabolic risk.

MATERIALS AND METHODS

The established Western Australian Pregnancy Cohort (Raine) study (http://www.rainestudy.org.au) was designed to measure the relationships between early life events and subsequent health and behavior (18). This is one of the largest and most closely followed prospective cohorts of pregnancy, childhood, and adolescence in the world. This study was approved by the Raine Executive Committee and the ethics committee of King Edward Memorial Hospital.

The follow-up performed at 14 years of age of the Western Australian pregnancy cohort involved anthropometry, resting BP, and fasting blood samples. Fasting blood samples were analyzed for serum insulin, glucose, triglycerides (TGs), cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and C-reactive protein (CRP). Glucose was measured by automated Technicon Axon Analyzer (Bayer Diagnostics, Pymble, Australia) with use of a hexokinase method. Insulin was measured by automated RIA (Tosoh Corporation, Tokyo, Japan). Total cholesterol and TG were determined enzymatically on the Cobas MIRA analyzer (Roche Diagnostics, Castle Hill, Australia) with reagents from Trace Scientific (Melbourne, Australia). High-density lipoprotein cholesterol was determined on heparin-manganese supernatant (19). The HDL_2 and HDL_3 cholesterol were determined with use of single precipitation (20). Low-density lipoprotein cholesterol was calculated with use of the Friedewald formula (21), valid for TG <3.5 mmol/L (for conversion to conventional units divide by 0.0113). C-reactive protein used a high-sensitivity monoclonal antibody assay (Dade Behring Marburg GmbH, Hessen, Germany) with interassay precision of 2.1% to 2.6% for values 0.5 to 14 mg/L.

Homeostasis model assessment (HOMA) was calculated by fasting insulin (microunits per milliliter) × fasting glucose (millimoles per liter)/22.5 (22), and IR was defined by a HOMA reading >4 (22) (for conversion to conventional units for concentration of glucose divide by 0.0555). Resting BP readings were taken with use of an oscillometric sphygmomanometer (Dinamap vital signs monitor 8100, Dinamap XL vital signs monitor, Dinamap Procare 100 [DPC100X –EN]; Critikon Corporation, Tampa, FL) after children were seated. The Dinamap was set to record readings automatically every 2 minutes. The mean of the second and third readings was calculated after the exclusion of the first reading.

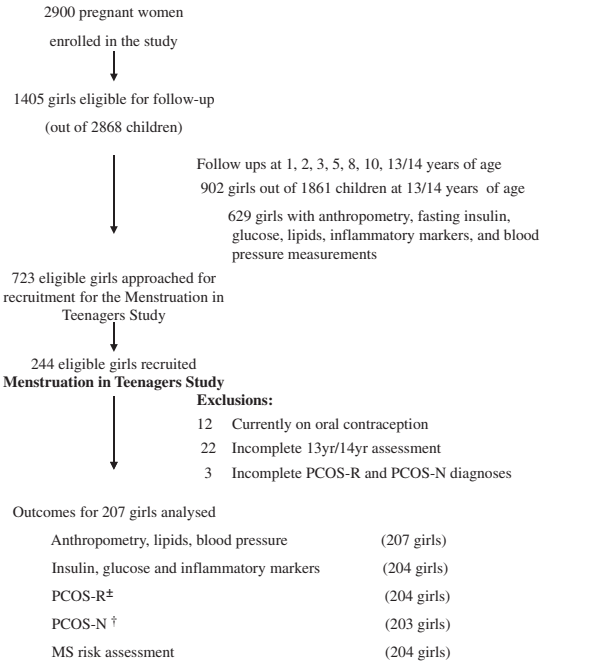
The metabolic syndrome in this cohort was defined by a modified International Diabetic Federation (IDF) (23), European Group for the Study of Insulin Resistance (EGIR) (24), the modified Adult Treatment Panel III (ATP III) (25, 26), and the World Health Organization (WHO) (27) definitions. These definitions rely on arbitrary adult cutoffs. There is no standardized accepted measure of the metabolic syndrome in adulthood, let alone adolescence (28). Therefore, an alternative approach, two-step cluster analysis also was used (29, 30). It is a particularly effective tool of use at defining groups taking into account variables for which there is strong evidence of clustering, Cluster analysis is best applied to data with natural groupings. When it is known that obesity, hypertension, dyslipidemia, and IR cluster closely (31), this technique is highly suitable for defining groups, reflecting the natural structure of the data without relying on age-inappropriate arbitrary cutoffs. Within a single cluster, the subjects are relatively homogeneous, sharing similar traits and being dissimilar to subjects in other clusters. The technique uses a scalable cluster analysis algorithm (32) designed specifically to handle large data sets and has been used previously to analyze variables within this cohort (29, 30). It preselects subjects into subclusters before further grouping into the desired number of clusters with use of log-likelihood distance. The cluster groups were formed with use of waist circumference, TGs, HDL, LDL, glucose, insulin, and BP. This technique was used previously in 14-year-olds and a subset of children aged 8 years to define a distinct high-risk group with features consistent with metabolic syndrome (29, 30).

Waist circumference was defined as abnormal by exceeding the 90th centile with use of a recognized age-related range derived from an Australian adolescent population (33), and the BP measurements were defined as abnormal by exceeding the 90th centile with use of the entire Raine cohort of adolescent females at the time of assessment. Subsequently to the metabolic assessment, all postmenarchal girls in the cohort aged 14 to 16 years were invited to participate in a study of menstruation in teenagers (4, 34–37). The study visit was scheduled for the second, third, fourth, or fifth day of their menstrual cycle. This ensured that subjects with regular and irregular cycles were sampled during the early follicular phase. All visits were timed between 3:30 PM and 4:30 PM. Subjects were given a menstrual diary to record all episodes of bleeding and spotting over the next 90 days. Age at menarche in this cohort has been reported previously (38).

Diagnosis of PCOS was ascertained with use of the Rotterdam consensus statement (39, 40), as the presence of two of the following: PCO morphology (41), clinical or biochemical hyperandrogenism, or oligo-ovulation or anovulation. The PCOS National Institutes of Health (NIH) criteria (42) were met if menstrual cycles were oligo-ovulatory or anovulatory together with either clinical or biochemical hyperandrogenism (for further detail on methods see supplementary material online or reference 37).

FIGURE 1

Flow chart of participants through the Western Australian Pregnancy Cohort (Raine cohort) assessments. PCOS-R = PCOS defined by the Rotterdam consensus statement (39, 40), as the presence of two of the following: PCO morphology (41), clinical or biochemical hyperandrogenism, or oligo-ovulation or anovulation. †PCOS-NIH = PCOS defined by the NIH criteria (42) were met if menstrual cycles were oligo-ovulatory or anovulatory together with either clinical or biochemical hyperandrogenism.



PCOS -R ± PCOS defined by the Rotterdam consensus statement (39-40), as the presence of two of the following: PCO morphology (41); clinical or biochemical hyperandrogenism; or oligo-anovulation.

PCOS- NIH † PCOS defined by the NIH criteria (42) were met if menstrual cycles were oligo-anovulatory together with either clinical or biochemical hyperandrogenism

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TABLE 1

With use of the cutoffs provided by the modified IDF reference ranges for metabolic parameters, the number and percentage of adolescents with readings outside the reference range by presence of PCOS, and prevalence of metabolic syndrome by the various definitions.

Measurement	All (n = 207)[a]	Non-PCOS–Rotterdam (n = 143)	PCOS–Rotterdam (n = 61)	*P* value	Non-PCOS–NIH (n = 169)	PCOS–NIH (n = 34)	*P* value
Waist circumference >90th percentile for age (33), no. (%)	82 (39.6)	42 (29.4)	28 (45.9)	.035[b]	49 (29.0)	21 (61.8)	.001[c]
Triglycerides >1.7 mmol/L, no. (%)	12 (5.8)	8 (5.6)	4 (6.6)	.754	10 (5.9)	2 (5.9)	.999
Glucose >5.6 mmol/L, no. (%)	4 (1.9)	2 (1.4)	2 (3.3)	.585	3 (1.8)	1 (2.9)	.523
BP >125/70 mm Hg, no. (%)[d]	5 (2.4)	3 (2.1)	2 (3.3)	.636	4 (2.4)	1 (2.9)	.999
HDL <1.03 mmol/L, no. (%)	21 (10.1)	11 (7.7)	10 (16.4)	.078	15 (8.9)	2 (5.9)	.131
BMI, mean (SD)	22.8 (3.8)	22.1 (2.9)	24.2 (5.1)	.005[b]	22.1 (2.0)	25.8 (5.8)	.001[c]
Metabolic syndrome							
IDF (ages 10 to <16 y), no. (%)	9 (4.3)	6 (4.2)	3 (4.9)	.999	7 (4.1)	2 (5.9)	.648
IDF, no. (%)	4 (1.9)	2 (1.4)	2 (3.3)	.586	2 (1.2)	2 (5.9)	.131
WHO, no. (%)	2 (1.0)	1 (0.7)	1 (1.6)	.510	1 (0.6)	1 (2.9)	.308
EGIR, no. (%)	5 (2)	1 (0.7)	4 (6.6)	.029[b]	1 (0.6)	4 (11.8)	.003[c]
ATP III, no. (%)	1 (0.5)	—	1 (1.6)	.299	—	1 (2.9)	.167
High–risk cluster for metabolic syndrome, no. (%)[e]	39 (18.8)	22 (15.4)	16 (26.2)	.079	26 (15.4)	12 (35.3)	.014[c]

[a] Percentages may be <100%.
[b] Excluding three cases of insufficient data for diagnosis of PCOS on Rotterdam criteria.
[c] Excluding four cases with insufficient data for diagnosis of PCOS on NIH criteria.
[d] Ninetieth centile for BP measurements from the females in the Raine cohort assessed in adolescence.
[e] The cluster groups were formed with use of waist circumference, TGs, HDL, LDL, glucose, insulin, and BP to derive distinct high-risk group with features consistent with metabolic syndrome. For conversion to conventional units divide by the following factors: TGs 0.0113, glucose 0.0555, HDL 0.0259.

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Statistical Analysis

Continuous data were summarized with use of means and SD or medians and interquartile ranges according to data normality. Categorical data were summarized with use of frequency distributions. Univariate group comparisons were conducted with use of Mann-Whitney or *t*-tests for continuous outcomes and χ^2 tests for categorical outcomes. Logistic regression was used to examine associations for HOMA and elevated liver enzymes, adjusting for other characteristics of interest. The cluster groups were formed with use of waist circumference, TGs, HDL, LDL, glucose, insulin, and BP as previously described. All hypothesis tests were two-sided, and P values $< .05$ were considered statistically significant. SPSS statistical software (version 15.0; SPSS, Inc., Chicago, IL) was used for data analysis.

RESULTS

Seven hundred twenty-three girls from the Raine cohort were approached to participate in the menstruation in teenagers study, of whom 244 agreed to take part; 71% had a normal BMI, 20% were overweight, and 9% were obese. Participating subjects were aged between 14.5 and 17.7 years. Seventy-three percent of participants were >2 years after menarche (mean age at menarche 12.5 years). Of the 244 participants, 207 had fasting blood samples available (Fig. 1). The prevalence of the metabolic syndrome in the unselected cohort of girls who agreed to take part in the menstruation in teenagers study with use of the EGIR, WHO, modified ATP, IDF, and the modified IDF definitions for metabolic syndrome in adolescents was 2.0% (n = 5), 1.0% (n = 2), 0.5% (n = 1), 1.9% (n = 4), and 4.3% (n = 9), respectively (Table 1). Comparisons of the characteristics: BMI, TG, HDL-C, systolic and diastolic BP, insulin, fasting glucose, cholesterol, and presence of metabolic syndrome with use of the different definitions between the 244 girls who were recruited and 479 girls who were not recruited, showed no statistical differences between the groups. The only exception was age at menarche, where the recruited girls reached menarche earlier than those who chose not to participate (mean age 12.5 vs. 12.9 years).

Of the girls recruited to this study PCOS diagnosis was met by 61 (29.5%) and 34 (16.4%) girls for Rotterdam and NIH PCOS diagnostic criteria, respectively. Of the 207 girls recruited to this study, menstrual irregularity was present in 110 (53.1%). Polycystic ovary morphology was present in 73 (35.3%), and an elevated calculated free T (FT) level was present in 54 (27.7%). With application of either the Rotterdam or NIH diagnostic criteria, the presence of PCOS was associated with higher insulin concentrations than in girls without PCOS (see Table 2). In applying the risk for metabolic syndrome by cluster analysis based on characteristics that define metabolic syndrome with the addition of insulin, 39 (18.8%) girls were classified as at "high risk" for the metabolic syndrome overall. The results of the cluster analysis by definition of PCOS are recorded in Table 1. Earlier age of menarche was not associated with an increased risk for being at a high metabolic risk by univariate analysis (P=.504) or when controlling for BMI (P=.952). A higher concentration of circulating calculated FT and a lower sex hormone–binding globulin (SHBG) concentration were associated with high metabolic risk (both P<.001 univariate) that was no longer significant after controlling for BMI (respective P values of P=.468 and P=.267). Total T concentrations were not associated with an increase in metabolic risk (P=.093). Calculated FT, total T, and SHBG all were associated with IR by univariate analysis and no longer statistically significant with a simultaneous adjustment for BMI as a continuous variable. Higher levels of circulating calculated FT were predictive of IR after controlling for being overweight and for obesity (P=.02 odds ratio [OR] 4.5, confidence intervals [CI] 1.3–16.1) but were not predictive of metabolic cluster after controlling for BMI (P=.31, OR 1.62, CI

TABLE 2

Markers of IR, metabolic risk, and inflammation.

Measurement	All (n = 207)	Non-PCOS–Rotterdam	PCOS–Rotterdam	*P* value	Non-PCOS–NIH	PCOS–NIH	*P* value
Insulin (μU/mL)	10.60 (3.48–64.7)	10.50 (7.90–13.00)	11.10 (8.70–14.95)	.045[a]	10.30 (7.94–13.05)	11.95 (9.16–16.60)	.014[a]
HOMA[b]	2.15 (0.58–11.79)	2.10 (1.58–2.73)	2.31 (1.58–2.73)	.058	2.10 (1.63–2.73)	2.50 (1.80–3.38)	.016[a]
Insulin resistant, no. (%)[b]	13 (6.4)	4 (2.8)	8 (13.6)	.007[a]	6 (3.6)	6 (18.2)	.006[a]
High risk for metabolic syndrome, no. (%)[b]	38 (18.6)	22 (15.4)	16 (26.2)	.079	26 (15.4)	12 (35.3)	.014[a]
OR (95% CI) for metabolic syndrome after controlling for BMI		1.00	1.81 (0.57–5.84)	.318	1.00	1.15 (0.30–4.45)	.844
CRP (mg/L)	0.26 (0.1–42.4)	0.24 (0.1–0.66)	0.40 (0.10–0.69)	.454	0.24 (0.1–0.68)	0.52 (0.18–0.71)	.117

Note: Measurements recorded are medians (interquartile ranges) or medians [ranges]. CRP = C-reactive protein; HOMA = homeostasis model assessment insulin (Fasting insulin [μU/mL] × Fasting glucose [mM]/22.5.

[a] Significant.

[b] Comparisons exclude four cases with glucose >5.6 mmol/L.

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0.64–4.1). BMI was related significantly to free T concentrations ($r = 0.53$, $P<.001$). After exclusion of four girls with a fasting blood glucose concentration >5.6 mmol/L, the prevalence of IR for BMI ≥25 was 25.0% (10 of 40 girls) versus 1.8% (3 of 163 girls) for BMI <25 ($P<.001$). Body mass index ≥27 as a predictor of IR had sensitivity of 76.9% and specificity of 23.1%, and BMI >27 as a predictor of IR had a sensitivity of 76.9% and a specificity of 92.1%, $P<.001$. The arbitrary cutoff for BMI >27 was selected because of the associated improvement in specificity, from 84.2% to 92.1%, of predicting IR.

Polycystic ovary syndrome diagnosis was associated with IR, by both Rotterdam criteria (OR 5.37, CI 1.55–18.61, $P=.008$) and NIH criteria (OR 5.93, CI 1.78–19.72, $P=.004$); however, both associations were no longer statistically significant with the adjustment for BMI (Rotterdam criteria adjusted OR 2.18, CI 0.51–9.26, $P=.292$, and NIH criteria adjusted OR 1.46, CI 0.30–7.12, $P=.643$). Neither menstrual irregularity nor PCO morphology was associated with IR (56.3% vs. 52.9%, $P=.795$, and 60.0% vs. 34.4%, $P=.055$, respectively). Although menstrual irregularity and having a high FT (PCOS-NIH criteria) were associated significantly with being at high risk for metabolic cluster ($P=.05$, OR 3.00, CI 1.3–6.4), the significance was lost when controlled for BMI. The most important predictor of metabolic cluster was being overweight ($P<.001$, OR 9.4, CI 3.5–25.2) and obese ($P<.001$, OR 40.7, CI 10.1–156.1). The association of various demographic, menstrual, and metabolic parameters analyzed and their relation to metabolic clustering are listed in Table 3. Adolescents with PCOS by both diagnoses had an elevated median serum CRP level compared with girls without PCOS, although not reaching statistical significance, 0.40 mg/L versus 0.24 mg/L ($P=.454$) and 0.52 versus 0.24 ($P=.117$) for Rotterdam criteria and NIH criteria, respectively (Table 2).

DISCUSSION

The principal finding of this study is that, of the recognized features of PCOS, an elevated FT level is the most significant variable predicting the presence of IR and is independent of obesity, in agreement with previous studies (13–15). Applying adult criteria for PCOS diagnosis in adolescent girls did not identify girls at risk for the metabolic syndrome reliably; indeed an elevated BMI was the strongest indicator of metabolic syndrome risk factors.

The clinically relevant findings are that, despite the low prevalence of metabolic syndrome in adolescent girls with PCOS with

TABLE 3

Characteristics found within "low-risk" and "high-risk" clusters.

Characteristic	All (n = 207)	"Low-risk metabolic syndrome" (n = 168)	"High-risk metabolic syndrome" (n = 39)	*P* value
At 13–year metabolic assessment				
Age at assessment (y)	14.1 [13.5–14.5]	14.1 [14.0–14.2]	14.1 [14.0–14.2]	.395
Years since menarche	−1.0 [−3.1–4.1]	−1.0 [−1.4–0.8]	−0.9 [−1.3–0.8]	.797
Waist circumference (cm)	73.0 [58.6–109.0]	71.4 [66.8–76.4]	85.0 [77.5–90.7]	<.001[a]
Systolic BP (mm Hg)	110 [84–150]	108 [102–113]	117 [113–120]	<.001[a]
Diastolic BP (mm Hg)	60 [43–74]	59 [53–83]	63 [59–66]	<.001[a]
HDL (mmol/L)	1.42 [0.72–2.50]	1.46 [1.26–1.66]	1.28 [1.06–1.50]	.003[a]
LDL (mmol/L)	2.30 [1.21–4.30]	2.30 [1.91–2.70]	2.41 [2.00–3.00]	.254
Triglycerides (mmol/L)	0.96 [0.45–2.77]	0.94 [0.73–1.16]	1.16 [0.89–1.36]	.001[a]
Cholesterol (mmol/L)	4.30 [3.1–6.27]	4.33 [3.76–4.70]	4.26 [3.83–4.82]	.815
CRP (mg/L)	0.26 [0.10–42.40]	0.24 [0.10–0.54]	0.58 [0.19–1.03]	.005[a]
Insulin (mU/L)	10.60 [3.48–64.7]	9.99 [7.92–12.88]	13.20 [11.00–19.70]	<.001[a]
Glucose (mmol/L)	4.70 [3.90–6.20]	4.70 [4.40–4.90]	4.70 [4.40–4.90]	.816
HOMA[b]	2.17 [0.65–11.79]	2.08 [1.65–2.71]	2.76 [2.21–4.44]	<.001[a]
HOMA >4, no. (%)[b]	16 (7.7)	5 (3.0)	11 (28.2)	<.001[a]
At recruitment to menstruation in teenagers study				
Age at recruitment (y)	15.1 [14.5–17.7]	15.1 [14.9–15.4]	15.1 [15.0–15.5]	.183
Age at menarche (y)	12.5 [9.1–16.1]	12.6 [12.0–13.3]	12.4 [11.4–13.0]	.066
Years since menarche	2.6 [0.3–7.0]	2.4 [1.8–3.2]	2.8 [2.2–3.6]	.023[a]
BMI	22.1 [17.1–40.1]	21.6 [19.8–23.4]	26.8 [24.1–29.3]	<.001[a]
Waist circumference (cm)	74.0 [62.0–122.0]	72.0 [68.9–76.5]	84.0 [81.0–92.0]	<.001[a]
Waist/hip ratio	0.86 [0.50–1.17]	0.86 [0.8–0.90]	0.88 [0.83–0.92]	.013
Systolic BP (mm Hg)	100 [80–130]	100 [90–110]	110 [100–118]	<.001[a]
Diastolic BP (mm Hg)	62 [50–90]	60 [60–70]	70 [60–76]	<.001[a]
PCOS diagnoses, no. (%)				
Irregular periods	110 (53.1)	85 (50.6)	25 (64.1)	.128
cFT ≥24.45 pmol/L	54 (26.1)	37 (22.0)	17 (43.6)	.002[a]
PCO morphology	73 (35.3)	61 (36.3)	12 (30.8)	.586
PCOS–Rotterdam, no. (%)	61 (29.5)	45 (26.8)	16 (41.0)	.079
PCOS–NIH, no. (%)	34 (16.4)	22 (13.1)	12 (30.8)	.014[a]

Note: Data shown are medians [minimum–maximum]. For conversion to conventional units divide by the following factors: HDL, LDL, and cholesterol 0.0259, TGs 0.0113, glucose 0.0555, FT 0.347. cFT = calculated free T; HOMA = homeostasis model assessment insulin (Fasting insulin [μU/mL] × Fasting glucose [mmol/L]/22.5).

[a] Significant.

[b] Comparisons exclude four cases with glucose >5.6 mmol/L.

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use of arbitrary cutoffs, they have a higher prevalence of the features of metabolic syndrome on cluster analysis. The most significant variable influencing the presence of IR, metabolic cluster, and an increased CRP was BMI.

There are at least eight potential definitions of the metabolic syndrome for use in children and adolescents (23–28, 43); however, the prevalence of metabolic syndrome in our cohort of adolescent girls with PCOS with use of the established definitions was low, and hence analysis of those girls at high risk for the metabolic syndrome by cluster analysis was performed. Despite having different emphases in the definition of metabolic syndrome, current definitions for the metabolic syndrome rely on arbitrary cutoffs of continuous variables, in themselves linearly related to cardiovascular risk, and use cutoffs designed for adult populations that are not suitable for use in children or adolescents. Therefore, using a technique such as cluster analysis allows risk to be defined without the use of cutoffs. The larger proportion that falls into the high-risk group with use of cluster analysis compared with the other definitions may be advantageous in analyses of population studies, because an increase in the number of high-risk cases leads to the increased power for detecting differences between the high- and low-risk groups. Our analysis demonstrated that girls with an elevated FT level are significantly more likely to be insulin resistant than girls without an elevated FT level, even after controlling for their BMI. This may have significant consequences for these girls in later life because of the subsequent risk for diabetes, cardiovascular disease, and nonalcoholic fatty liver resulting from childhood IR (44). Furthermore, all of the more "adverse" metabolic parameters are clustered within the "high risk" of metabolic syndrome, and girls with an elevated FT level and PCOS by NIH criteria tended to be clustered in the high-risk group (Table 3).

Our results demonstrate that an adolescent girl with hyperandrogenism and menstrual irregularity (PCOS-NIH) seen by her general practitioner has a one in three chance of being in the high-risk metabolic cluster; if she is overweight or obese that risk is increased substantially. Consequently this complaint presents a unique opportunity potentially to influence the girls' diet and lifestyle; however, evidence suggests that this opportunity rarely is taken (45). More than one third of adolescent girls will complain of menstrual irregularity, increasing with increasing BMI (46, 47), and ultimately one third of Australian adolescent girls will be seen by their general practitioner with a menstrual complaint (48), presenting a unique opportunity for intervention.

Our study is in agreement with the principal finding of the study in overweight girls with PCOS (12), where BMI was the most significant variable influencing the presence of metabolic syndrome. In this study 53% of overweight girls with PCOS-NIH met the criteria for metabolic syndrome, and 55% of obese or overweight girls without evidence of PCOS met the criteria for metabolic syndrome. Although a much smaller percentage of our patients were overweight than in that study, we believe our findings complement those findings. The significant difference identified by Rossi et al. (12) was that the area under the curve insulin and glucose were significantly greater for girls with PCOS-NIH compared with those of their counterparts without PCOS. Our study also demonstrated increased HOMA levels for girls with PCOS by Rotterdam and NIH criteria, before controlling for BMI. A recent retrospective clinic-based study in adolescent girls from Italy also concluded that metabolic derangements were related to an elevated BMI and not to the presence of PCOS-Rotterdam (16).

Of the cohort of 723 available girls only 244 attended for assessment of menstrual function, potentially leading to selection bias in terms of those more likely to be having menstrual problems. However, this may have been offset by a "healthy" selection bias. This was a challenging study for participants, requiring recording of menstrual bleeding patterns for 3 months, an ultrasound examination, and blood tests to be synchronized with the early follicular phase only on weekdays and at specific hours to fit in with school commitments.

This study of metabolic parameters in a representative Western Australian cohort suggests that a significant number of girls with PCOS exists with clustering of features of metabolic syndrome and a raised CRP level. In particular overweight girls with PCOS-NIH are at substantially increased risk for development of metabolic syndrome and present an opportunity for research into intervention to protect their long-term health. Whether early intervention with lifestyle changes or with medical therapy may ameliorate these features over the long term remains to be elucidated.

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SUPPLEMENTAL MATERIAL

MATERIALS AND METHODS

Polycystic ovary morphology was assessed by transabdominal ultrasound evaluation of ovarian size and morphology performed by one of two experienced gynecologic ultrasonographers. All images were evaluated by one expert. Polycystic ovary morphology was defined according to standard international criteria, that is, one or more ovaries >10 cm^3 or ≥ 12 follicles between 2 and 9 mm in diameter (41). The presence of ovulation was assessed by initially screening with a prospective menstrual diary, collected over 3 months, to establish menstrual regularity. Irregular cycles were defined as those <25 or >35 days in duration or where the cycle length varied from month to month by >4 days (43). Other causes of oligo-ovulation or anovulation were excluded by measuring TSH and PRL concentrations. Clinical hyperandrogenism was assessed by the presence of hirsutism, with use of the Ferriman-Gallwey scoring system (44). Biochemical hyperandrogenism was defined as concentrations in the upper 25th centile of free T (calculated FT), which was ≥ 24.45 pmol/L (conversion factor to conventional units divide by 0.347 for picograms per deciliter) for this data set. Sex hormone–binding globulin was measured by immunoassay with use of a noncompetitive liquid-phase immunoradiometric assay (SHBG-IRMA kit; Orion Diagnostica, Espoo, Finland): interassay and intrapatients coefficients of variation 2.0% to 8.6% and 15.4%, respectively. Total T was measured by RIA (Repromed Laboratory, Adelaide, Australia) (lower limit of sensitivity 0.347 nmol/L; normal female range 0.5–2.5 nmol/L; conversion factor to conventional units divide by 0.347 for nanograms per deciliter) (45). The intraassay and interpatient coefficients of variation are 6% and 15% at the 1 nmol/L concentration, respectively. Calculated FT was calculated from the measured total T and SHBG concentrations with use of standardized methods (46) (http://www.issam.ch/freetesto.htm).

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