

Hormonal Profile of Women with Self-Reported Symptoms of Oligomenorrhea and/or Hirsutism: Northern Finland Birth Cohort 1966 Study

SAARA TAPONEN, HANNU MARTIKAINEN, MARJO-RIITTA JÄRVELIN, JAANA LAITINEN, ANNELI POUTA, ANNA-LIISA HARTIKAINEN, ULLA SOVIO, MARK I. McCARTHY, STEPHEN FRANKS, AND AIMO RUOKONEN

Departments of Clinical Chemistry (S.T., A.R.) and Obstetrics and Gynecology (S.T., H.M., A.-L.H.), University of Oulu and Oulu University Hospital, 90014 Oulu, Finland; Department of Public Health Science and General Practice (S.T., M.-R.J., A.P., U.S.), University of Oulu, 90014 Oulu, Finland; Oulu Regional Institute of Occupational Health (J.L.), 90220 Oulu, Finland; Department of Epidemiology and Public Health (M.-R.J., U.S.), Imperial College Faculty of Medicine, W2 1PG London, United Kingdom; Imperial College Genetics and Genomics Research Institute (M.I.M.), Imperial College Faculty of Medicine, W12 0NN London, United Kingdom; and Department of Reproductive Science and Medicine (S.F.), Institute of Reproductive and Developmental Biology, Imperial College of Science Technology and Medicine, W12 0NN London, United Kingdom

The hormonal profiles of nested female patients ($n = 500$) with self-reported symptoms typical of polycystic ovary syndrome (PCOS), oligomenorrhea, and/or hirsutism and their randomly selected controls ($n = 1026$) at the age of 31 yr were analyzed in a general population-based Northern Finland birth cohort 1966 to find out whether the symptomatic women also have the endocrine characteristics of PCOS and could be detected in a general population using simple questions. Higher medians of serum testosterone (T) (2.10 vs. 1.90 nmol/liter, $P < 0.001$), LH (5.40 vs. 4.85 U/liter, $P = 0.005$), insulin (53.8 vs. 51.66 pmol/liter, $P = 0.040$), and free androgen index (FAI) (4.01 vs. 3.03, $P < 0.001$) and lower glucose/insulin ratio (91.1×10^8 vs. 94.9×10^8 , $P = 0.048$) and SHBG (52.4 vs. 60.7 nmol/liter, $P < 0.001$) were observed among the cases, but no difference was observed in cortisol and glucose levels between the cases and controls. Of all the women in the cohort, 10.2% reported only oligomenorrhea and had biochemical findings similar to the whole case group. Those who reported only hirsutism (10.4%) were in between the case and control groups according to biochemical findings. The subjects who reported both oligomenorrhea and hirsutism (3.4%) had the highest T, LH,

FAI, insulin, and glucose and the lowest SHBG and glucose/insulin ratio, compared with the case group and the groups with either symptom only indicating a dose-response manner in typical endocrine profile of PCOS by adding up symptoms. The levels of T and FAI were higher and SHBG lower in groups with overweight or obesity both at 14 and 31 yr, compared with groups with normal weight at 14 yr and overweight or obesity at 31 yr. In the group with normal weight at 14 and 31 yr and the group with overweight or obesity at 14 yr but normal weight at 31 yr, the levels of T and FAI were lowest and SHBG highest. T and FAI were higher and SHBG lower among the cases than the controls in groups stratified by weight development from adolescence to adulthood. In conclusion, this longitudinal study of a large, stable population indicates that women with self-reported symptoms of hirsutism and/or oligomenorrhea show endocrine characteristics of PCOS and can be detected in a general population using simple questions. These symptoms are markers of the underlying metabolic alterations possibly associated with increased health risks in later life. (*J Clin Endocrinol Metab* 88: 141-147, 2003)

OLIGOMENORRHEA AND HIRSUTISM are symptoms typical of polycystic ovary syndrome (PCOS), the most common endocrine disorder among women of fertile age (1, 2), the etiology of which is not fully understood. Polycystic ovaries have been found in about 20% of women at aged 30-35 yr who have not sought help for gynecological symptoms (3). Over 90% of women with polycystic ovaries who had not sought help for their symptoms, examined in a study of normal women, had at least one symptom (irregular menses, hirsutism) that could be considered a clinical marker of PCOS (4). The typical endocrine profile of women with PCOS includes increased levels of serum testosterone (T) and LH and decreased levels of SHBG (5), which correlate with hyperinsulinemia and obesity (5, 6). Hyperinsulinemia, an elevated LH level, and a reduced SHBG level have been

detected already in adolescent girls with signs of hyperandrogenism (7). However, the endocrine features in PCOS are heterogeneous (8), and the identification of women at risk of developing PCOS is not simple.

Obesity, insulin resistance, and hyperinsulinemia are strongly associated with PCOS (9, 10). Independent of obesity, women with PCOS have cardiovascular risk factors (11, 12). The diagnosis of PCOS in early adulthood would be important to focus on prevention of possible future consequences associated with the syndrome, such as infertility and type 2 diabetes in addition to cardiovascular risk.

The previous studies are mostly based on hospital populations, and to our knowledge no general population-based longitudinal studies on markers or predictors of PCOS exist. We studied a birth cohort of almost 6000 women in Northern Finland (13) to find out the correlation of self-reported symptoms of hirsutism and/or oligomenorrhea with biochemical

Abbreviations: BMI, Body mass index; FAI, free androgen index; PCOS, polycystic ovary syndrome; T, testosterone.

findings. Our *a priori* hypothesis was that simple, symptom-based questions are useful to trace women with an endocrine profile typical for PCOS and insulin resistance and thus at risk to develop long-term consequences on health. Because obesity is one of the most important factors that influences clinical and biochemical presentation of women with polycystic ovaries, we stratified the analyses by body mass index categories as well as by weight gain between the ages of 14 and 31 yr to explore their possible modifying effect on natural history of PCOS.

Materials and Methods

Study population

The nested case-control study population derives from a 1966 Northern Finland birth cohort followed since the sixth month of their mother's pregnancy until the offspring's age of 31 yr. In 1966, 5964 females were born, 5889 alive. At 14 yr of age, the teenagers answered a postal inquiry. In 1997-1998, 5687 of them were alive and traced for the 31-yr follow-up study when a postal questionnaire was sent to all women. Women still living in the original target or capital city area ($n = 4074$) were invited for a clinical examination. Of these, 3077 women gave a blood sample and written consent and filled in the postal questionnaire on the symptoms. The questions were: 1) Is your menstrual cycle often more than (over twice a year) 35 d? and 2) Do you have excessive growth of body hair? Of the women who returned the questionnaire ($n = 4523$), 24% reported symptoms of hirsutism and/or oligomenorrhea (including subjects with amenorrhea), 10.4% reported hirsutism alone, 10.2% reported oligomenorrhea alone, and 3.4% reported both symptoms. Those women who used hormonal

contraception ($n = 859$), were pregnant ($n = 211$), or used medication for diabetes ($n = 13$) were excluded from the data. Those who reported symptoms were defined as cases. For each case, two controls were selected randomly from the same birth cohort. The final case-control study included 500 cases and 1026 controls (Fig. 1).

Blood samples and laboratory methods

The blood samples were drawn after overnight fasting in the morning (between 0800 and 1100 h). Blood glucose samples were stored in +4 C until analyzed during the same day. Serum insulin samples were stored in -20 C and were analyzed within 7 d of sampling. The T, SHBG, LH, and cortisol samples were stored in -80 C until analyzed. Free androgen index (FAI) was calculated by [testosterone] \times 100 divided by [SHBG]. Those who had reported eating, drinking, or smoking during the fasting time ($n = 42$) were excluded from the statistical analyses of glucose and insulin.

The concentrations of SHBG and LH were analyzed by fluoroimmunoassay (Wallac, Inc. Ltd., Turku, Finland), T by automated chemiluminescence system (ACS-180, Ciba-Corning, Inc., Medfield, MA), cortisol (Orion Diagnostica, Oulunsalo, Finland), and insulin (Pharmacia Diagnostics, Uppsala, Sweden) by RIA, and blood glucose by a glucose dehydrogenase method (Granutest 250, Diagnostica Merck, Darmstadt, Germany). The intra- and interassay coefficients of variation were 1.3% and 5.1% for SHBG, 4.9% and 6.5% for LH, 4.0% and 5.6% for T, 4.0% and 4.3% for cortisol, 5.3% and 7.6% for insulin, and 1.5% and 2.3% for blood glucose. The sensitivity of the insulin assay was 14.35 pmol/liter and of the T assay 0.35 nmol/liter.

Body mass index (BMI) and gain

BMI (kg/m^2) was calculated at ages 14 and 31 yr. Overweight and obesity at 14 yr were defined as a BMI at or above the 85th or 95th

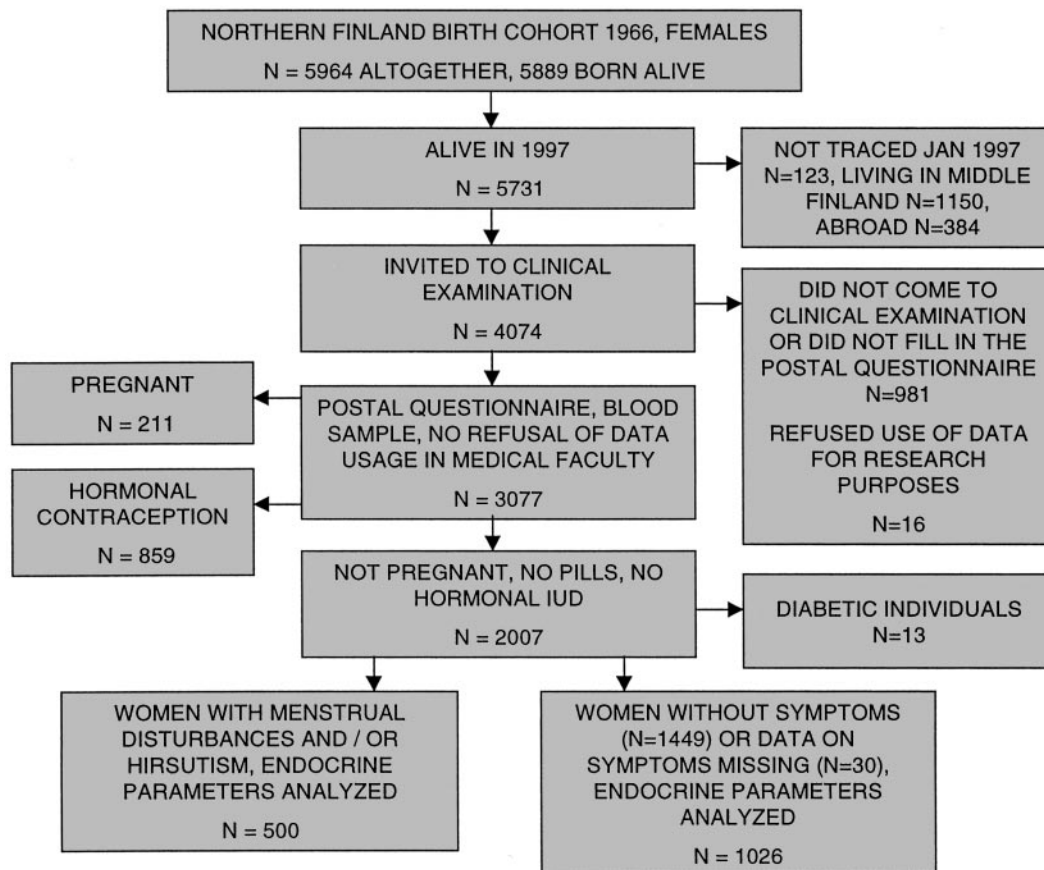


FIG. 1. The flow chart for the nested case-control study on hormonal profile in the 1966 Northern Finland birth cohort.

percentile, respectively. Adult BMI at 31 yr was classified as: normal weight (<25 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥30.0 kg/m²). The subjects were also divided into four subgroups according to their weight development from adolescence to adulthood: 1) normal weight at 14 and 31 yr, 2) normal weight at 14 yr and overweight or obese at 31 yr, 3) overweight or obese at 14 yr and overweight or obese at 31 yr, and 4) overweight or obese at 14 yr and normal weight at 31 yr.

Statistics

Distribution of each outcome variable was skewed to the right both among the cases and controls. Consequently, medians and quartiles are reported and the differences in distributions were tested with the non-parametric Mann-Whitney *U* test.

Statistical analyses were performed (version 10.1 for Windows; SPSS, Inc., Chicago, IL).

Results

Biochemical findings of all cases and controls and those who reported hirsutism alone, oligomenorrhea alone, and both symptoms

The hormone levels in the cases, controls, and subjects who reported oligomenorrhea alone (O-group), hirsutism alone (H-group), and both symptoms (OH-group) are presented in Table 1 as medians and lower and upper quartiles. The T, LH, and insulin levels as well as FAI were significantly higher, but SHBG levels alone were lower in the case group than the control group. The only significant difference between the O-group and H-group was observed in LH, which was significantly higher in the O-group. Comparing the H-group to the OH-group or O-group to the OH-group, significantly higher medians of T, LH, FAI, and insulin were observed in the OH-group than H-group or in O-group. The glucose/insulin ratio was significantly lower among the cases than among the controls and lowest in the OH-group. The O- and H-groups did not differ significantly from the whole case

group in glucose/insulin ratio. Neither the glucose nor cortisol levels differed significantly among any of the groups.

Biochemical findings of cases and controls by BMI

The hormone levels stratified by BMI categories are presented for the cases and controls in Table 2 as medians and lower and upper quartiles. Of the case (control) subjects, 61% (67%) were normal weight, 25% (23%) overweight, and 14% (10%) obese. T and FAI levels were significantly higher but SHBG levels lower among the normal, overweight, and obese cases than among their controls, and they changed in a dose-response manner by increasing BMI category. The difference between the case and control groups remained, independent of BMI. LH levels were significantly higher among the cases than controls only in the group with normal weight. Cortisol levels did not differ between the cases and controls in any of the BMI categories. Insulin and glucose levels increased with increasing BMI, but the cases and controls did not differ from each other in any of the BMI categories. The glucose/insulin ratio decreased with increasing BMI, but there was no statistically significant difference between the cases and controls in any BMI category studied.

Adult SHBG, T, and FAI values by weight development from adolescence to adulthood

Figure 2 illustrates T, SHBG, and FAI differences (medians, interquartile ranges) between the cases and controls by weight development from adolescence to adult 31 yr. The subjects were divided into four subgroups according to whether they remained normal weight or overweight or obese, gained overweight or obesity, or lost weight from overweight or obesity to normal weight. The figures indi-

TABLE 1. The hormonal findings of the cases and the controls and subgroups with symptoms of oligomenorrhea alone, hirsutism alone, and both

	Cases (n = 500) ^a	Controls (n = 1026) ^b	P ^c	Reported only oligomenorrhea (n = 207–215)	Reported only hirsutism (n = 200–207)	Reported both oligomenorrhea and hirsutism (n = 72–74)	P ^d	P ^e	P ^f
T (nmol/liter)	2.10 (1.60, 2.70)	1.90 (1.40, 2.40)	^g	2.10 (1.50, 2.70)	2.00 (1.50, 2.50)	2.50 (1.90, 3.23)	NS	^g	^g
SHBG (nmol/liter)	52.4 (36.3, 72.3)	60.7 (44.2, 81.0)	^g	52.4 (35.8, 69.4)	56.3 (41.3, 77.6)	38.4 (27.4, 61.5)	NS	^h	^g
LH (U/liter)	5.40 (3.40, 8.40)	4.85 (3.30, 7.13)	^h	6.20 (3.93, 8.68)	4.20 (2.90, 6.90)	6.45 (4.38, 11.6)	^g	NS	^g
Cortisol (μmol/liter)	0.36 (0.27, 0.47)	0.36 (0.27, 0.47)	NS	0.35 (0.25, 0.46)	0.36 (0.28, 0.46)	0.39 (0.26, 0.53)	NS	NS	NS
FAI	4.01 (2.47, 6.29)	3.03 (2.06, 4.54)	^g	3.95 (2.48, 5.77)	3.53 (2.26, 5.80)	5.90 (3.92, 9.87)	NS	^g	^g
Insulin (pmol/liter)	53.8 (42.3, 68.2)	51.7 (43.1, 64.1)	^h	53.1 (42.3, 68.9)	53.1 (43.8, 65.9)	59.2 (45.9, 86.8)	NS	^h	^h
Glucose (mmol/liter)	4.90 (4.70, 5.20)	4.90 (4.70, 5.20)	NS	4.90 (4.60, 5.20)	4.90 (4.70, 5.20)	5.00 (4.80, 5.20)	NS	NS	NS
Glucose/insulin (×10 ⁶)	0.91 (0.74, 1.14)	0.95 (0.77, 1.11)	^h	0.92 (0.74, 1.16)	0.92 (0.78, 1.13)	0.84 (0.56, 1.13)	NS	NS	^h

The values are expressed as medians (Q₂₅, Q₇₅). The significance test used is the Mann-Whitney *U* test. The number of individuals in separate analyses varies due to missing values.

^a n (glucose) = 490, n (insulin) = 485, n (glucose/insulin) = 485.

^b n (glucose) = 991, n (insulin) = 990, n (glucose/insulin) = 986.

^c Cases *vs.* controls.

^d Only oligomenorrhea *vs.* only hirsutism.

^e Only oligomenorrhea *vs.* both symptoms.

^f Only hirsutism *vs.* both symptoms.

^g *P* < 0.001.

^h *P* < 0.05.

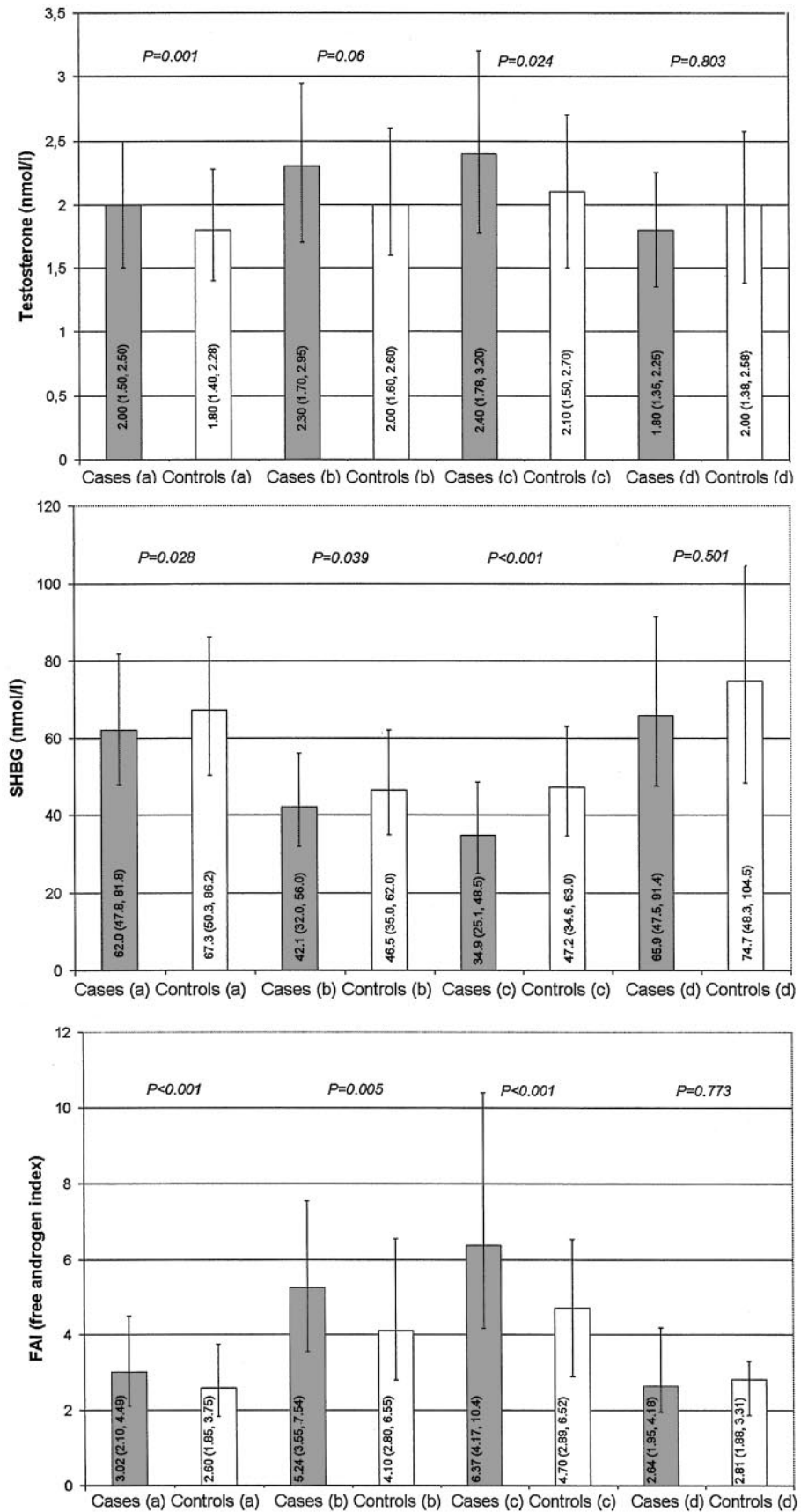


FIG. 2. Adult T, SHBG, and FAI values by weight development from adolescence to adulthood. a, Normal weight at 14 and 31 yr [n (cases) = 251, n (controls) = 596]; b, normal weight at 14 yr, overweight or obese at 31 yr [n (cases) = 117, n (controls) = 184]; c, overweight or obese at 14 and 31 yr [n (cases) = 74, n (controls) = 119]; d, overweight or obese at 14 yr and normal weight at 31 yr [n (cases) = 22, n (controls) = 36].

through to adult life. Because the women who used oral contraceptives or hormonal treatment had to be excluded from the study, it is possible that the individuals with the most severe symptoms and biochemical findings having sought help were left out. This exclusion is, however, likely to dilute the differences between the cases and the controls, which highlights the importance of our findings.

In this study, the median insulin level was significantly higher among the cases than controls. When stratified by BMI categories, the serum insulin levels increased and the glucose/insulin ratio decreased with increasing BMI in both cases and controls, but within the weight categories, insulin levels did not differ significantly between the cases and controls. The glucose/insulin ratio, considered a marker for insulin resistance (21), was, however, significantly lower among the cases than the controls. The levels of SHBG were clearly lower among the cases than the controls throughout all weight categories, which obviously is related to decreased insulin sensitivity and higher insulin secretion in these women (10). It is well documented that insulin secretion is increased, even in lean PCOS subjects (22–24) and hyperinsulinemia directly reduces serum SHBG levels in PCOS women (25). Hence, SHBG acts as a useful marker of insulin secretion and insulin resistance (26, 27). In accordance with this study, serum SHBG level was shown to be highly effective as a single marker in one epidemiological study for detecting women with PCOS (28). When we compared the cases and controls between the 25% quartile and 75% quartile SHBG concentrations, insulin for the case group was significantly higher in the low SHBG quartile, but T levels did not differ significantly between the quartiles, suggesting that insulin is the major regulator of serum SHBG levels (data not shown).

Body size in adolescence and adulthood was shown to be positively associated with PCOS symptoms in our study population. Holte *et al.* (5) showed that the negative effects of PCOS and obesity on SHBG levels were independent of each other, whereas T and FAI were affected by obesity only in women with PCOS. In this study, the serum T level seemed to be affected by both PCOS symptoms and obesity. The T levels were higher in case groups throughout all BMI categories, compared with controls, and they increased with increasing BMI in a dose-response manner among both the cases and controls. This effect was also seen in the FAI levels, which also increased with increasing BMI in both the case and control groups, and the difference between symptomatic cases and nonsymptomatic controls was seen in all weight categories.

Weight at 14 yr and its later development predicts the future metabolic changes at the age of 31 yr. In the cases and controls who were normal by weight at 14 and 31 yr, T and FAI were lowest and SHBG highest at 31 yr. The metabolic changes were less favorable in the cases and controls who were normal by weight at the age of 14 and overweight or obese at the age of 31 yr and most unfavorable in those who were overweight or obese both at the age of 14 and 31 yr. In the weight development categories where the subjects remained stable weight or gained overweight or obesity, the cases had higher T and FAI and lower SHBG levels than the controls. The cases and the controls who were overweight or

obese at 14 but normal weight at 31 yr had levels of T, SHBG, and FAI similar to the group with normal weight at 14 and 31 yr, suggesting that weight reduction could be beneficial and may prevent unfavorable metabolic changes. The differences in hormone levels between the weight development groups probably are due to, at least partly, the differences in BMI because those cases who were overweight already at the age of 14 yr had the highest BMI.

Elevated serum concentrations of LH are common in women with PCOS (29). In this study there was a significant difference in the serum LH levels between the cases and controls only in the normal weight group, but in overweight and obese women, the difference disappeared. The serum LH levels tended to decrease with increasing weight in the case group but in the control group LH stayed at the same level. This finding is in accord with those of previous studies that have shown an inverse relationship between LH and BMI (5, 30).

In this study, using serum cortisol as an indicator of adrenal steroid production, we could not demonstrate any difference in the adrenal steroidogenesis between the symptomatic cases and controls. However, in the clinically more severe cases of PCOS, cortisol and adrenal androgen secretion is clearly increased (31).

In conclusion, this study shows that self-completed questions concerning oligomenorrhea and hirsutism are useful in detecting women with typical endocrine features of PCOS and signs of decreased insulin sensitivity. Of biochemical markers, SHBG seems to be most useful as an additional screening tool. The unfavorable changes in the endocrine and metabolic parameters, also recorded among the overweight and obese controls, were magnified in the presence of PCOS symptoms, and they may be considered risk factors for health in later life. Special attention, weight reduction and possibly medical treatment, should be paid to the symptomatic overweight or obese women, in whom the most profound changes were observed.

Acknowledgments

Received June 25, 2002. Accepted October 1, 2002.

Address all correspondence and requests for reprints to: Saara Taponen, M.D., Department of Clinical Chemistry, University of Oulu, PL 5000, University of Oulu, 90014 Oulu, Finland. E-mail: saara.taponen@mail.suomi.net.

This work was supported by the Academy of Finland and European Commission, Quality of Life and Management of Living Sources Programme, contract QLGI-CT-2000-01643.

References

1. Franks S 1995 Polycystic ovary syndrome. *N Engl J Med* 333:853–861
2. Dunaif A, Thomas A 2001 Current concepts in the polycystic ovary syndrome. *Annu Rev Med* 52:401–419
3. Koivunen R, Laatikainen T, Tomas C, Huhtaniemi I, Tapanainen J, Martikainen H 1999 The prevalence of polycystic ovaries in healthy women. *Acta Obstet Gynecol Scand* 78:137–141
4. Polson DW, Wadsworth J, Adams J, Franks S 1988 Polycystic ovaries—a common finding in normal women. *Lancet* 1:870–872
5. 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* 41: 473–481
6. Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Ronsisvalle E, Guido M, Caruso A, Lanzone A 1999 Impact of insulin and body mass index on

- metabolic and endocrine variables in polycystic ovary syndrome. *Metabolism* 48:167–172
7. **Apter D, Butzow T, Laughlin A, Yen SSC** 1995 Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. *J Clin Endocrinol Metab* 80:2966–2973
 8. **Conway GS, Honour JW, Jacobs HS** 1989 Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol* 30:459–470
 9. **Nestler JE, Clore JN, Blackard WG** 1989 The central role of obesity (hyperinsulinemia) in the pathogenesis of the polycystic ovary syndrome. *Am J Obstet Gynecol* 161:1095–1097
 10. **Dunaif A, Segal KR, Futterweit W, Dobrjansky A** 1989 Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38:1165–1174
 11. **Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborovski JV, Remsberg KE, Kuller LH** 2000 Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 20:2414–2421
 12. **Mather KJ, Kwan F, Corenblum B** 2000 Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. *Fertil Steril* 73:150–156
 13. **Rantakallio P** 1988 The longitudinal study of the Northern Finland Birth Cohort of 1966. *Paediatr Perinat Epidemiol* 2:59–88
 14. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R** 1998 Prevalence of the polycystic ovary syndrome in unselected black and white women of the Southeastern United States: a prospective study. *J Clin Endocrinol Metab* 83:3078–3082
 15. **Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF** 2000 A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 85:2434–2438
 16. **Adams J, Polson DW, Franks S** 1986 Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J* 293:355–359
 17. **Hull MG** 1987 Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gynecol Endocrinol* 1:235–245
 18. **O'Driscoll JB, Mantora H, Higginson J, Pollock A, Ken J, Anderson DC** 1994 A prospective study of the prevalence of clear-cut endocrine disorders and polycystic ovaries in 350 patients with hirsutism and androgenic alopecia. *Clin Endocrinol (Oxf)* 41:231–236
 19. **Franks S** 1989 Polycystic ovary syndrome: a changing perspective. *Clin Endocrinol (Oxf)* 31:87–120
 20. **Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, Zapanti ED, Bartzis MI** 1999 A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 84:4006–4011
 21. **Legro RS, Finegood D, Dunaif A** 1998 A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 83:2694–2698
 22. **Morales AJ, Laughlin GA, Butzow T, Maheshwari H, Baumann G, Yen SSC** 1996 Insulin, somatotrophic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinctive features. *J Clin Endocrinol Metab* 81:2854–2864
 23. **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 ovary syndrome. *Hum Reprod* 6:1266–1274
 24. **Toprak S, Yonem A, Cakir B, Guler S, Azal O, Ozata M, Corakci A** 2001 Insulin resistance in nonobese patients with polycystic ovary syndrome. *Horm Res* 55:65–70
 25. **Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN, Blackard WG** 1991 A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 72:83–89
 26. **Yki-Jarvinen H, Mäkimattila S, Utriainen T, Rutanen EM** 1995 Portal insulin concentrations rather than insulin sensitivity regulate serum sex hormone-binding globulin and insulin-like growth factor binding protein 1 *in vivo*. *J Clin Endocrinol Metab* 80:3227–3232
 27. **Nestler JE** 1993 Sex hormone-binding globulin: a marker for hyperinsulinemia and/or insulin resistance? *J Clin Endocrinol Metab* 76:273–274
 28. **Escobar-Morreale HF, Asuncion M, Calvo RM, Sancho J, San Millan JL** 2001 Receiver operating characteristic analysis of the performance of basal serum hormone profiles for the diagnosis of polycystic ovary syndrome in epidemiological studies. *Eur J Endocrinol* 145:619–624
 29. **Yen SSC, Vela P, Rankin J** 1970 Inappropriate secretion of follicle-stimulating hormone and luteinizing hormone in polycystic ovarian disease. *J Clin Endocrinol Metab* 30:435–442
 30. **Taylor AE, McCourt B, Martin KA, Anderson EJ, Adams JM, Schoenfeld D, Hall JE** 1997 Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 82:2248–2256
 31. **Martikainen H, Salmela P, Nuojuua-Huttunen S, Perälä J, Leinonen S, Knip M, Ruokonen A** 1996 Adrenal steroidogenesis is related to insulin in hyperandrogenic women. *Fertil Steril* 66:564–570