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Presence of metabolic risk factors in non-obese PCOS sisters: Evidence of heritability of insulin resistance

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ABSTRACT. This study was performed to determine whether phenotypically healthy sisters of women with polycystic ovary syndrome (PCOS) have evidence of insulin resistance. We studied 54 women: 17 with PCOS, 17 sisters of these probands and 20 control women with similar age, body mass index (BMI) and waist-to-hip ratio (WHR). The PCOS sisters had neither clinical nor laboratory evidence of hyperandrogenism. However, estimated insulin resistance indices indicated decreased insulin sensitivity in PCOS sisters compared with the controls. No difference of insulin resistance indices was detected between the PCOS and their sisters. This finding provides additional evidence that there is a hereditary trait regarding insulin resistance in the PCOS families. (J. Endocrinol. Invest. 27: 931-936, 2004)

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder of unknown etiology affecting approximately 4-6% of reproductive-aged women (1, 2). It is characterized by chronic anovulation and hyperandrogenism (3). In addition, important metabolic aberrations, like insulin resistance (4), impaired glucose intolerance (IGT), Type 2 diabetes (T2D) (5, 6), dyslipidemia, coagulopathy (7), hypertension and an estimated 7-fold increased risk for cardiovascular disease have been associated with PCOS (5, 6, 8). Insulin resistance and hyperinsulinemia play important roles in the pathogenesis of PCOS (4). Moreover, β-cell insulin secretory defects are present in women with PCOS (9, 10), which are most evident among a subset of patients who have a first degree relative with T2D (9). However, the mode of inheritance of PCOS and the associated metabolic and steroidogenic abnormalities have not been elucidated.

Familial aggregation of PCOS consistent with a genetic trend has been documented (11-15): some studies support a single dominant gene with high penetrance, others do not; autosomal (14-18) as well as X-linked (19) dominant modes of inheritance have also been suggested. Family studies of PCOS have focused on ovarian morphology (18), menstrual irregularities, and symptoms of hyperandrogenism and hyperandrogenemia (HA) (11, 13, 20). Recently, interest has been focused on mode of insulin resistance inheritance in PCOS families (20-22).

Norman et al., who studied the families of five patients with PCOS, reported that increased insulin levels were common among first degree relatives (22). Heritability of β-cell dysfunction has been identified in families of women with PCOS (23). Legro et al. have shown that there are three reproductive phenotypes in the sisters of women with PCOS: 1) chronic anovulation and HA consistent with typical PCOS, 2) HA with regular menses and apparently normal fertility and 3) "unaffected" by the syndrome sisters. They reported that PCOS sisters who presented with HA, with or without regular menstrual cycles (20, 24), had high insulin levels and low fasting glucose-to-insulin ratios (20). However, other studies have suggested that women with HA and regular cycles were not insulin resistant (25-27).

The primary aim of the present study was to investigate the metabolic and hormonal parameters in non-obese PCOS sisters who are normoandrogenemic and clinically "unaffected" by the syndrome.

Key-words: PCOS, PCOS families, PCOS sisters, insulin resistance, hyperinsulinemia.

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MATERIALS AND METHODS

Subjects

The study consisted of 54 women who were all recruited from the outpatient Department of Endocrinology, of Laiko University Hospital in Athens. The study protocol was approved by the local ethics board and informed consent was obtained from all participants. All the participants in the study, for at least 3 months, were off any medication known to affect carbohydrate or sex hormone metabolism. Seventeen women [mean age: 23.52±1.01 yr; body mass index (BMI): 24.94±1.59 kg/m^2] with the diagnosis of PCOS were studied. Their diagnosis was based, according to the National Institute of Child Health and Human Development Conference, on the presence of irregular menstrual cycles (≤8 menses per yr), elevated serum levels of testosterone (T) or free T (fT) and with clinical symptoms of hyperandrogenism. Non-classical congenital adrenal hyperplasia, androgen secreting neoplasm, hyperprolactinemia, and thyroid disease were excluded by appropriate tests in the PCOS women as well as in their sisters. Seventeen sisters of these probands (mean age: 22.88±0.93 yr; BMI: 22.98±1.16 kg/m^2) were studied. The control group consisted of twenty asymptomatic healthy women (mean age: 24.95±0.86 yr; BMI: 22.19±0.96 kg/m^2). The sisters of PCOS and the controls had no evidence of hyperandrogenism (hirsutism, acne or alopecia) on physical examination; both groups had regular menstrual cycles (intermenstrual intervals between 25 and 35 days but with no more than 4 days variation from cycle to cycle), and had not sought treatment for menstrual disturbances, infertility, or hirsutism at any time.

The women studied in each group had similar age and BMI by design of the study.

Study protocol

Weight, height, waist and hip circumferences were measured. BMI [=weight (kg)/height (cm) ^{2}] and WHR [=waist circumferences (cm)/hip circumferences (cm)] were calculated. The evaluations were conducted within the follicular phase of the menstrual cycle in control women and at any time in the PCOS women who were chronically anovulatory. In the amenorrheic women, recent ovulation was excluded by progesterone measurement (<5 nmol/l). Blood samples were collected at 08:00 to 10:00 h after an overnight fast.

Biochemical parameters

Blood samples were collected at 08:00 h after an overnight fast to determine serum levels of total T (nmol/l), fT (pmol/l), SHBG (nmol/l), DHEAS (μmol / L), serum fasting insulin (INS, pmol/L), serum fasting glucose (GLU, mmol/l), FSH (IU/L), LH (IU/L), total cholesterol (TC, mmol/l), triglycerides (TG, mmol/l), HDL (mmol/l), and uric acid (UA, mmol/l) were measured.

The LH-to-FSH ratio was estimated by the formula: LH/FSH.

The free androgen index (FAI, %) was estimated by the formula:

$$FAI = (\text{total T}/SHBG) \times 100$$

Insulin resistance estimation

Insulin resistance was estimated by the glucose-to-insulin ratio (GLU/INS), the quantitative insulin sensitivity check index (QUICKI) and the homeostasis model assessment (HOMA).

QUICKI is defined as:

$$QUICKI = 1/[\log(\text{fasting insulin}) + \log(\text{fasting glucose})] \quad (28)$$

HOMA is applied by using the following formula:

$$HOMA = [\text{fasting insulin } (\mu U/ml) \times \text{fasting glucose } (mmol/l)]/22.5 \quad (29)$$

Assay methods

Blood samples were centrifuged immediately, and serum was stored at –20 C until assayed. The samples were assayed within three months from the collection.

Plasma glucose was determined by the glucose oxidase method (Glucose Analyser, Beckman Coulter, Inc., Palo Alto, CA). TC, TG and HDL were determined using techniques of Spectrum FPX (Abbott Laboratories, North Chicago, IL), whereas LDL was calculated by the Friedewald equation. Plasma UA was determined by uricase/PAP method. Serum insulin levels were determined using the RIA INSULIN-CT Kits (CIS-Bio International, Gif-sur-Yvette, Cedex, France). Duplicate plasma samples were analyzed for total T measured using the DSL-4000 RIA Kit (Diagnostic Systems Laboratories, Inc., Webster, TX). Duplicate plasma samples were analyzed for fT using the commercially available Coat-A-Count FT Kit (Diagnostic Products, Los Angeles, CA). SHBG serum levels were measured by an immunoradiometric assay using the SHBG ^{125}I (Radim S.A., Liege, Belgium). DHEAS serum levels were measured by DSL DHEAS RIA Kit (DSL Diagnostic Systems Laboratories, Inc., Webster, TX). LH and FSH were measured using the LHsp and FSH IRMA kits from Biosource Technologies, Inc., Europe S.A. The intra- and interassay coefficients of variance for low and high levels, respectively, were: a) for insulin, 8.2 and 8.8% and 5.4 and 6.4%; b) for total T, 9.6 and 8.6% and 8.1 and 9.1%; c) for fT, 4.3 and 5.5% and 3.2 and 3.4%; d) for SHBG, 5.1 and 5.1% and 5.6 and 4.6%; e) for LH, 6.5 and 8.8% and 3.5 and 4.5%; f) for FSH, 2.7 and 5.3% and 1.6 and 3.6%; g) for DHEAS, 9.4 and 6.3% and 9.6 and 9.9%.

Statistical analysis

Results are reported as mean value±SE. The statistical analysis of the difference in hormonal and metabolic profile between the three groups was assessed using multiple analyses of variance (ANOVA). Statistical analysis was accepted at a p value <0.05. Analysis was performed using Statistical package for the Social Sciences (SPSS, version 11.01; Spss, Inc., Chicago, IL) for Windows XP (Microsoft Corp.).

RESULTS

The women studied in each group did not differ in age and BMI by design of the study – PCOS: 23.52±1.01 yr and 24.94±1.59 kg/m^2, sisters: 22.88±0.93 yr and 22.98±1.16 kg/m^2, controls: 24.95±0.86 yr and 22.19±0.96 kg/m^2. WHR did not vary between groups – PCOS: 0.73±0.018, sisters: 0.72±0.014, controls: 0.72±0.015.

T levels were different with statistical significance between PCOS and sisters (2.99±0.26 vs 1.74±0.17 nmol/l, p<0.0001) and PCOS and controls (2.99±0.26 vs 1.31±0.09 nmol/l, p<0.0001). The sisters when compared with controls had higher T levels, but without statistical significance (p=ns). fT levels were statistically dissimilar between PCOS and sisters (10.78±1.07 vs 6.27±0.90 pmol/l,

$p<0.001$) and PCOS and controls (10.78±1.07 vs 6.10±0.48 pmol/l, $p<0.001$) but not between sisters and controls. DHEAS was similar between groups (PCOS: 3.61±1.08 μmol/l, sisters: 3.13±1.05 μmol/l, controls: 2.19±0.69 μmol/l) as well as SHBG levels, but the latter were lower in the PCOS and higher in the controls (PCOS: 33.70±3.72 nmol/l, sisters: 36.27±4.46 nmol/l, controls: 42.56±3.56 nmol/l). FSH (PCOS: 6.88±0.58 IU/l, sisters: 6.67±1.04 IU/l, controls: 6.46±0.80 IU/l), LH (PCOS: 10.18±2.01 IU/l, sisters: 7.74±1.70 IU/l, controls: 5.64±0.81 IU/l), and LH/FSH (PCOS: 1.56±0.29, sisters: 1.32±0.32, controls: 1.00±0.18) did not differ between groups (Table 1).

INS was statistically different between PCOS and control group (109.94±18.04 vs 42.99±3.75 pmol/l, $p<0.01$), their sisters and control group (139.87±32.92 vs 42.99±3.75 pmol/l, $p<0.001$), but not between the PCOS and their sisters. GLU differed only between PCOS and their sisters (5.11±0.17 vs 4.60±0.15 nmol/l, $p<0.02$) but not between the other groups (controls: 4.83±0.13 nmol/l). UA (PCOS: 230.78±17.25 nmol/l, sisters: 237.33±22.00 nmol/l, controls: 215.91±17.25 nmol/l); TC (PCOS: 4.70±0.27 nmol/l, sisters: 4.63±0.31 nmol/l, controls: 4.22±0.18 nmol/l); HDL (PCOS: 1.31±0.09 mmol/l, sisters: 1.25±0.09 mmol/l, controls: 1.19±0.11 mmol/l); and LDL (PCOS: 2.96±0.33 mmol/l, sisters: 2.55±0.25 mmol/l, controls: 2.67±0.24 mmol/l) did not differ between groups. TG differ only between PCOS and controls (1.15±0.25 vs 0.62±0.05 mmol/l, $p<0.02$; sisters: 0.78±0.09 mmol/l) (Table 2).

FAI index differed with statistical significance between PCOS and sisters (324.88±61.19% vs 195.74±44.34%, $p<0.03$), and PCOS and controls (324.88±61.19% vs 103.19±13.14%, $p<0.0001$]. The sisters, when compared with controls, had higher value of FAI index, but without statistical significance (p=ns) (Table 1).

The PCOS and their sisters difference is statistically significant when compared with controls in all the indexes of insulin resistance GLU/INS, HOMA and QUICKI, but they do not differ between themselves. PCOS vs controls was: 7.45±1.15 vs 15.86±1.29,

Table 1 - *Hormonal profile of polycystic ovary syndrome (PCOS) patients (P), their sisters (S) and normal women (C).*

Variable	P	S	C	P vs C	P vs S	S vs C
T (nmol/l)	2.99±0.26	1.74±0.17	1.31±0.09	0.0001	0.0001	ns
fT (pmol/l)	10.78±1.07	6.27±0.90	6.10±0.48	0.001	0.001	ns
DHEAS (μmol/l)	3.61±1.08	3.13±1.05	2.19±0.69	ns	ns	ns
SHBG (nmol/l)	33.70±3.72	36.27±4.46	42.56±3.56	ns	ns	ns
FSH (IU/l)	6.88±0.58	6.67±1.04	6.46±0.80	ns	ns	ns
LH (IU/l)	10.18±2.01	7.74±1.70	5.64±0.81	ns	ns	ns
LH/FSH	1.56±0.29	1.32±0.32	1.00±0.18	ns	ns	ns
FAI (%)	324.88±61.19	195.74±44.34	103.19±13.14	0.0001	0.03	ns

Data are given means±SE, $p<0.05$ statistically significant. T: Testosterone; fT: free T; FAI: free androgen index.

Table 2 - *Metabolic profile of polycystic ovary syndrome (PCOS) patients (P), their sisters (S) and normal women (C).*

Variable	P	S	C	P vs C	P vs S	S vs C
Glucose (mmol/l)	5.11±0.17	4.60±0.15	4.83±0.13	ns	0.02	ns
Insulin (pmol/l)	109.94±18.04	139.87±32.92	42.99±3.75	0.01	ns	0.001
GLU/INS	7.45±1.15	7.98±1.68	15.86±1.29	0.0001	ns	0.0001
QUICKI	0.327±0.014	0.331±0.023	0.371±0.009	0.0001	ns	0.0001
HOMA	3.6±0.67	4.15±1.08	1.33±0.13	0.0001	ns	0.0001
UA (μmol/l)	230.78±17.25	237.33±22.00	215.91±17.25	ns	ns	ns
TC (mmol/l)	4.70±0.27	4.63±0.31	4.22±0.18	ns	ns	ns
HDL (mmol/l)	1.31±0.09	1.25±0.09	1.19±0.11	ns	ns	ns
LDL (mmol/l)	2.96±0.33	2.55±0.25	2.67±0.24	ns	ns	ns
TG (mmol/l)	1.15±0.25	0.78±0.09	0.62±0.05	0.02	ns	ns

Data are given means±SE, $p<0.05$ statistically significant. GLU/INS: glucose-to-insulin ratio; QUICKI: quantitative insulin sensitivity check index; HOMA: homeostasis model assessment; UA: uric acid; TC: total cholesterol; TG: triglycerides.

$p<0.0001$; 3.6±0.67 vs 1.33±0.13, $p<0.0001$; and 0.327±0.014 vs 0.371±0.009, $p<0.0001$, respectively; sisters vs controls was: 7.98±1.68 vs 15.86±1.29, $p<0.0001$; 4.15±1.08 vs 1.33±0.13, $p<0.0001$; and 0.331±0.023 vs 0.371±0.009, $p<0.0001$, respectively (Figs.1, 2).

DISCUSSION

In this study, it is demonstrated that non-obese phenotypically healthy young women, who are sisters of PCOS women, are hyperinsulinemic and have insulin resistance, assessed by mathematical indices, compared with normoandrogenic normovulatory women without PCOS family history.

Two important family studies, recently published, demonstrated that PCOS women and their sisters differ in insulin resistance. In the first study, by Legro et al., affected PCOS's sisters were compared with controls and had hyperinsulinemia and insulin resistance. Another group of PCOS's sisters, assigned as "unaffected", on the basis of androgen levels and menstrual cycles, had normal parameters of insulin action (when compared with control group). However, the "unaffected" sisters had lower BMI than the "affected" PCOS's sisters and the control group (20).

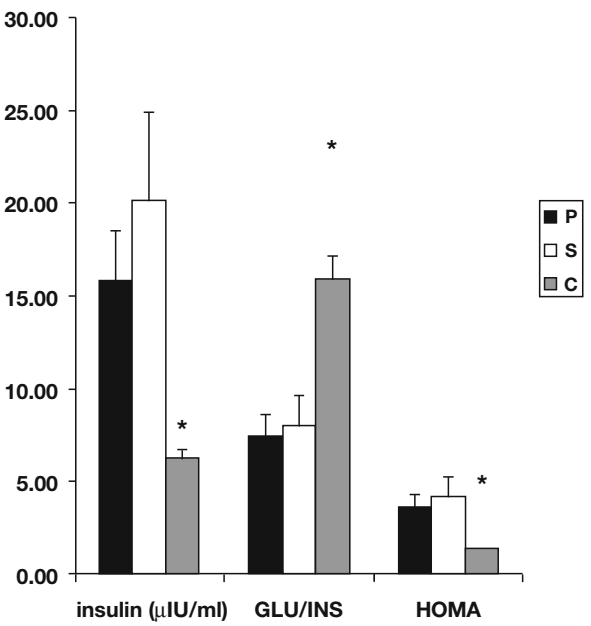

Fig. 1. The different values in insulin, glucose-to-insulin ratio (GLU/INS), and homeostasis model assessment (HOMA) between the three groups: polycystic ovary syndrome (PCOS) patients (P), their sisters (S) and normal women (C). $p<0.05$ *vs* P and s; conversion factor: μIU/ml x 7.175=pmol/l in SI units.

In the second study, from Yildiz et al., the investigators compared PCOS's sisters ("unaffected" and 16% "affected") with matched controls for BMI and age, and found an increased prevalence of glucose intolerance and insulin resistance (fasting insulin, area under the curve for insulin during the oral glucose tolerance test, HOMA index, GLU/INS) as well as higher androgen levels compared with the respective control group. Despite the fact that the sister's group was mixed with "unaffected" and "affected" women, it is important to notice that insulin resistance was still present in the subgroup analysis when the sisters with glucose intolerance were excluded (21).

Norman et al. have reported that hyperinsulinemia may be an important marker in the family members of PCOS patients, underlying the genetic trait, dependent or independent of the PCOS presence (22). Our study provides evidence that the presence of hyperinsulinemia and insulin resistance, independently of the presence of HA and menstrual disturbances, has a stronger trait in PCOS families.

This fact indicates that phenotypically normal sisters of women with PCOS can be at risk of developing IGT and T2D (30, 31). However, this finding should be interpreted with caution because hyperinsulinemia is a common trait in the general population, although studies in young ages have not been carried out (32). Nevertheless, the "unaffected" women may consist of a particularly vulnerable group of individuals predisposed to metabolic aberrations.

Hyperinsulinemia was not associated with other parameters of the metabolic syndrome (i.e. TG, HDL, LDL, TC): this could either be due to hyperinsulinemia preceding the expression of other parameters

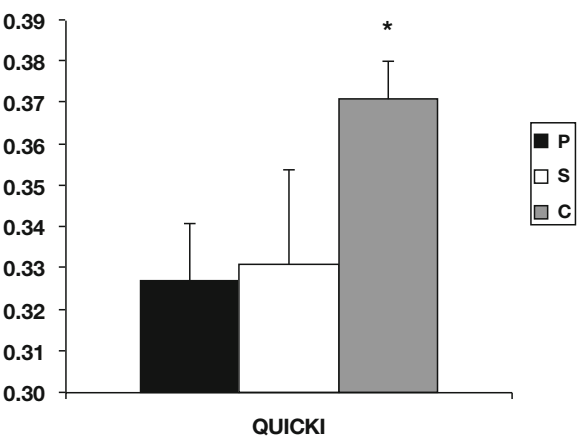

Fig. 2. The different values in quantitative insulin sensitivity check index (QUICKI) between the three groups: polycystic ovary syndrome (PCOS) patients (P), their sisters (S) and normal women (C). $p<0.05$ *vs* P and S.

of dysmetabolic syndrome, or to the full picture of the syndrome requiring environmental factors, such as obesity.

Diabetes screening in patients with PCOS is recommended according to the current American Diabetes Association guidelines (21, 32). Further data are required to support the idea of extending the diabetes screening to the sisters of PCOS patients, not only to "affected" (21), but even to "unaffected".

High prevalence of HA in PCOS female first-degree relatives with or without menstrual irregularity has also been reported (33, 34, 24). fT levels and FAI did not differ between the group of sisters and the controls. However, the androgen levels varied between the PCOS women and their sisters, maybe because the sisters did not have clinical signs of hyperandrogenism.

The interpretation of the PCOS studies should take into account both the heterogeneity of the syndrome and the ethnicity.

Among the limitations of our study it should be considered the small number of subjects studied and the assessment of insulin resistance with mathematical indices.

In summary, the present study demonstrates the presence of hyperinsulinemia and insulin resistance independently of the presence of HA and menstrual disturbances in PCOS "healthy" sisters when compared with normal women. It remains to be elucidated if this could be due to genetic and/or environmental factors. Further large scale, controlled family studies are warranted to delineate the risk of glucose intolerance and other metabolic complications as well as to propose screening and preventive strategies for the phenotypically healthy sisters of PCOS women.

REFERENCES

1. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998, 83: 3078-82.
2. Diamanti-Kandarakis E, Kouli C, Bergiele A, et al. A survey of the PCOS in the Greek island of Lesbos: Hormonal and metabolic profile. J Clin Endocrinol Metab 1999, 84: 4006-11.
3. Dunaif A, Givens JR, Haseltine FP, Merriam GR. Polycystic ovary syndrome. Current issues in endocrinology and metabolism. Boston: Blackwell, 1992.
4. Diamanti-Kandarakis E, Dunaif A. New perspectives in PCOS. Trends Endocrinol Metab 1996, 7: 267-71.
5. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999, 22: 141-6.
6. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999, 84: 165-9.
7. Diamanti-Kandarakis E, Palioniko G, Alexandraki K, Bergiele A, Koutsouba T, Bartzis M. The prevalence of 4G5G polymorphism of Plasminogen Activator Inhibitor-1 (PAI-1) gene in Polycystic Ovarian Syndrome and its association with plasma PAI-1 levels. Eur J Endocrinol 2004, 150: 795-800.
8. Dahlgren E, Janson PO, Johansson S, Lapidus L, Lindstedt G, Tengborn L. Hemostatic and metabolic variables in women with polycystic ovary syndrome. Fertil Steril 1994, 61: 455-60.
9. Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS. Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 1995, 96: 520-7.
10. Dunaif A, Finegood DT. ß-Cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 1996, 81: 942-7.
11. Legro RS, Spielman R, Urbanek M, Driscoll D, Strauss III JF, Dunaif A. Phenotype and genotype in polycystic ovary syndrome. Recent Prog Horm Res 1998, 53: 217-56.
12. Franks S, Gharani N, Waterworth D, et al. Genetics of polycystic ovary syndrome. Mol Cell Endocrinol 1998, 145: 123-8.
13. Legro RS. Polycystic ovary syndrome. Phenotype to genotype. Endocrinol Metab Clin North Am 1999, 28: 379-96.
14. Cooper H, Spellacy W, Prem K, Cohen W. Hereditary factors in the Stein-Levanthal syndrome. Am J Obstet Gynecol 1968, 100: 371-87.
15. Givens JR. Familial polycystic ovarian disease. Endocrinol Metab Clin North Am 1988, 17: 771-83.
16. Lunde O, Magnus P, Sandvik L, Hoglo S. Familial clustering in the polycystic ovarian syndrome. Gynecol Obstet Invest 1989, 28: 23-30.
17. Carey AH, Chan KL, Short F, White D, Williamson R, Franks S. Evidence of a single gene effect causing polycystic ovaries and male pattern baldness. Clin Endocrinol (Oxf) 1993, 38: 653-8.
18. Govind A, Obhrai MS, Clayton RN. Polycystic Ovaries Are Inherited as an Autosomal Dominant Trait: Analysis of 29 Polycystic Ovary Syndrome and 10 Control Families. J Clin Endocrinol Metab 1999, 84: 38-43.
19. Wilroy Jr RS, Given JR, Wiser WL, Coleman SA, Andersen RN, Summitt RL. Hyperthecosis: an inheritable form of polycystic ovarian disease. Birth Defects Orig Artic Ser 1975, 11: 81-5.
20. Legro R, Bentlet- Lewis R, Driscoll D, Wang SC, Dunaif A. Insulin resistance in the sisters of women polycystic ovary syndrome: association with hyperandrogenemia rather than menstrual irregularity. J Clin Endocrinol Metab 2002, 87: 2128-33.
21. Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, hyperandrogenemia in first degree

relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003. 88: 2031-6.

22. Norman RJ, Masters S, Hague W. Hyperinsulinemia is common in family members of women with polycystic ovary syndrome. Fertil Steril 1996, 66: 942-7.
23. Colilla S, Cox NJ, Ehrmann DA. Heritability of insulin secretion and insulin action in women with polycystic ovary syndrome and their first degree relatives. J Clin Endocrinol Metab 2001, 86: 2027-31.
24. Kahsar-Miller MD, Nixon C, Boots LR, Go RC, Azziz R. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. Fertil Steril 2001, 75: 53-8.
25. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab 1987, 65: 499-507.
26. Robinson S, Kiddy D, Gelding SV, et al. The relationship of insulin insensitivity to menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin Endocrinol (Oxf) 1993, 39: 351-5.
27. Walker BR, Rodin A, Taylor NF, Clayton RN. Endogenous inhibitors of 11ß-hydroxysteroid dehydrogenase type 1 do not explain abnormal cortisol metabolism in polycystic ovary syndrome. Clin Endocrinol (Oxf) 2000, 52: 77-80.
28. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000, 85: 2402-10.
29. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 1987, 79: 790-800.
30. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2001, 24: 89-94.
31. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. Diabetes 1995, 44: 1386-91.
32. American Diabetes Association. Screening for diabetes. Diabetes Care 2002, 25: 21-4.
33. Legro, RS, Driscoll, D, Strauss III JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci USA 1998, 95: 14956-60.
34. Franks S. Polycystic ovary syndrome. N Engl J Med 1995, 333: 853-61.